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Proposed Registration Decision PRD2012-20

Pyroxasulfone

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Overview

Proposed Registration Decision for Pyroxasulfone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Pyroxasulfone Technical and Pyroxasulfone 85 WG, containing the technical grade active ingredient pyroxasulfone, to control weeds in field corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Pyroxasulfone Technical and Pyroxasulfone 85 WG.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at healthcanada.gc.ca/pmra.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on pyroxasulfone, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on pyroxasulfone, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Pyroxasulfone?

Pyroxasulfone is a novel pre-emergence herbicide discovered amongst a series of herbicidal 3-sulfonylisoxazoline derivatives. Pyroxasulfone inhibits very-long-chain fatty acid (VLCFA) synthesis by interfering with elongation of the C18 chains, which are normally catalyzed by VLCFA elongases. This causes inhibition of shoot elongation after seed germination. Formation of cell membranes and waxy cuticle materials within developing plant tissue is also severely affected by lack of VLCFAs. The active ingredient, pyroxasulfone, enters target plants through root-uptake or via the apical meristem. This compound is primarily efficacious against annual grasses and also provides control of certain broadleaf weeds.

Pyroxasulfone is regarded as a Weed Science Society of America Group 15 Herbicide or Herbicide Resistance Action Committee Group K3 Herbicide.

Health Considerations

Can Approved Uses of Pyroxasulfone Affect Human Health?

Pyroxasulfone is unlikely to affect your health when used according to label directions.

Potential exposure to pyroxasulfone may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pyroxasulfone products are used according to label directions.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Pyroxasulfone was of low acute toxicity by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes and non-irritating to the skin. Pyroxasulfone was not considered to be a skin sensitizer. Consequently, no hazard signal words are required on the label.

The end-use product Pyroxasulfone 85 WG was of low acute toxicity via the oral, dermal and inhalation routes of exposure in rats, and was minimally irritating to the skin and eyes of rabbits. It was a skin sensitizer in guinea pigs. Consequently, the hazard signal words "POTENTIAL SKIN SENSITIZER" are required on the label.

Based on the weight of evidence, pyroxasulfone did not cause damage to genetic material. There was no indication that it causes birth defects in the developing young, or effects on the immune or reproductive systems. The target organs of toxicity following pyroxasulfone treatment included the liver, heart, kidney, skeletal muscle and peripheral nerves. Pyroxasulfone caused urinary bladder tumours in male rats at a high dose level. There was evidence that pyroxasulfone caused damage to the nervous system. When pyroxasulfone was given to pregnant or nursing animals, effects of a serious nature (changes in brain development) were observed on both the developing fetus and juvenile animal at doses that were not toxic to the mother, indicating that the young were more sensitive to pyroxasulfone than the adult animal. The risk assessment takes this sensitivity into account in determining the allowable level of human exposure to pyroxasulfone, and protects against the noted adverse effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and all infants (<1 year), the subpopulation which would ingest the most pyroxasulfone relative to body weight, are expected to be exposed to less than 93% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from pyroxasulfone is not of concern for all population sub-groups. There are no cancer risks of concern.

An aggregate (food and water) dietary intake estimate for the highest exposed population (all infants, <1 year old) used less than 54% (95th Percentile) of the acute reference dose, which is not a health concern.

The Food and Drugs Act (FDA) prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the Pest Control Products Act (PCPA). Food containing a pesticide residue at the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout the United States using pyroxasulfone on field corn are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation/Evaluation Document.

Occupational Risks From Handling Pyroxasulfone 85 WG

Occupational risks are not of concern when Pyroxasulfone 85 WG is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Pyroxasulfone 85 WG as well as field workers re-entering freshly treated fields can come in direct contact with pyroxasulfone residues on the skin. Mixers, loaders and applicators may also be exposed by breathing sprays and mists. Therefore, the label specifies that anyone mixing/loading and applying 41 kg or less of Pyroxasulfone 85 WG must wear a long-sleeved shirt, long pants and chemical-resistant gloves. Anyone mixing/loading more than 41 kg of Pyroxasulfone 85 WG must wear chemical-resistant coveralls over a long-sleeved shirt and long pants, and chemical-resistant gloves. Anyone applying more than 41 kg of Pyroxasulfone 85 WG must wear coveralls over a long-sleeved shirt and long pants and must apply in a closed cab tractor.

The label also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern. There are no cancer risks of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Pyroxasulfone Is Introduced Into the Environment?

Pyroxasulfone will enter the environment when applied once a year to field corn. Pyroxasulfone will dissipate in the environment primarily through leaching and gradual biotransformation to the major transformation product KIH-485-M-1. The risk to aquatic organisms can be mitigated with buffer zones.

Pyroxasulfone has low solubility and volatility. It is not expected to transform through hydrolysis or phototransformation. Pyroxasulfone and its major transformation product, KIH-485-M-1, are not expected to transform quickly in the terrestrial or aquatic environment through microbially mediated processes. In the aquatic environment, pyroxasulfone has a tendency to partition to the sediments where it gradually transforms into KIH-485-M-1, which re-solubilises to the water column and gradually accumulates. Pyroxasulfone and its major transformation product are considered to be persistent to moderately persistent in terrestrial and aquatic environments.

Pyroxasulfone and its major transformation product, KIH-485-M-1, do not adsorb strongly to soil particles and are expected to have high mobility in soil. Pyroxasulfone and KIH-485-M-1 are expected to dissipate quickly from the soil surface in the field. The major route of dissipation in the environment for pyroxasulfone and its major transformation product is expected to be leaching to ground water.

When applied using a ground boom sprayer, there is a potential for exposure of non-target organisms in the environment to pyroxasulfone and its major transformation product as a result of runoff and spray drift. Pyroxasulfone and its major transformation product, KIH-485-M-1, were practically non-toxic to most non-target organisms. Pyroxasulfone is highly toxic to aquatic plants, especially freshwater algae. The risk to these aquatic non-target organisms can be mitigated with buffer zones.

Value Considerations

Pyroxasulfone, as a pre-plant surface, pre-emergence treatment or an early post-emergence treatment on field corn, provides control of annual grasses and certain broadleaf weeds.

A single application of pyroxasulfone provides effective residual control of annual grasses, including barnyard grass, giant foxtail, yellow foxtail, green foxtail, Italian ryegrass, large crabgrass, and redroot pigweed and common waterhemp in all types of field corn in Canada.

Pyroxasulfone is compatible with integrated weed management practices in conservation and conventional crop cultivation systems.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Pyroxasulfone 85 WG to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with pyroxasulfone residues on the skin or through inhalation of spray mists, anyone mixing/loading and applying 41 kg or less of Pyroxasulfone 85 WG must wear a long-sleeved shirt, long pants and chemical-resistant gloves. Anyone mixing/loading more than 41 kg of Pyroxasulfone 85 WG must wear chemical-resistant coveralls over a long-sleeved shirt and long pants, and chemical-resistant gloves. Anyone applying more than 41 kg of Pyroxasulfone 85 WG must wear coveralls over a long-sleeved shirt and long pants and must apply in a closed cab tractor.

The label also requires that workers do not enter treated fields for 12 hours after application. In addition, standard label statements to protect against drift during application were added to the label.

Environment

Based on the risk identified to off-target sensitive habitats, buffer zones of 1 to 5 m are required to protect terrestrial and freshwater habitats, respectively.

Next Steps

Before making a final registration decision on pyroxasulfone, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

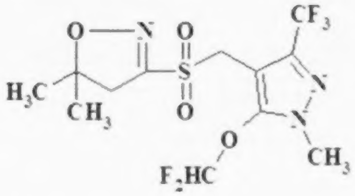
When the PMRA makes its registration decision, it will publish a Registration Decision on pyroxasulfone (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Pyroxasulfone

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Pyroxasulfone
Function	Herbicide
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	3-[(5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)pyrazol-4-ylmethylsulfonyl]-4,5-dihydro-5,5-dimethyl-1,2-oxazole
2. **Chemical Abstracts Service (CAS)**	3-[[[5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl]sulfonyl]-4,5-dihydro-5,5-dimethylisoxazole
CAS number	447399-55-5
Molecular formula	$C_{12}H_{14}F_5N_3O_4S$
Molecular weight	391.316 g/mol
Structural formula	
Purity of the active ingredient	99.2%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Pyroxasulfone Technical

Property	Result
Colour and physical state	White crystalline solid
Odour	Slight characteristic odour
Melting range	130.7°C
Boiling point or range	N/A
Density	1.60 g/cm^3
Vapour pressure at 25°C	2.4×10^{-6} Pa

Property	Result
Henry's law constant at 20°C	2.65×10^{-9} atm m^3/mol
Ultraviolet (UV)-visible spectrum	UV/VIS: at pH 1.13 $\lambda_{max} = 225.5$ nm $\varepsilon = 7291$ $Lmol^{-1}cm^{-1}$ at pH 7.23 $\lambda_{max} = 225.0$ nm $\varepsilon = 7340$ $Lmol^{-1}cm^{-1}$ at pH 10.91 $\lambda_{max} = 225.5$ nm $\varepsilon = 7334$ $Lmol^{-1}cm^{-1}$
Solubility in water at 20 ± 0.5°C	3.49×10^{-3} g/L
Solubility in organic solvents at 20°C (g/L)	Solvent Solubility Methanol 11.4 Acetone > 250 Ethyl acetate 97.0 n-Hexane 0.0721 Toluene 11.3 Dichloromethane 151
n-Octanol-water partition coefficient (K_{ow}) at 25°C	At pH = 8.7, log $K_{ow} = 2.39$
Dissociation constant (pK_a)	N/A
Stability (temperature, metal)	Showed no signs of degradation at elevated temperatures to any of the metals/metal ions tested.

End-Use Product - Pyroxasulfone 85 WG

Property	Result
Colour	Tannish to yellowish
Odour	Halide to alcoholic, earthy musk-like, burnt plastic odour
Physical state	Solid
Formulation type	Wettable granules
Guarantee	85%
Container material and description	High density polyethylene bottles, 6.5 L
Density	1.58 g/cm^3
pH of 1% dispersion in water	9.51
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agent.
Storage stability	Stable when stored for 12 months at ambient temperature in high density polyethylene bottles.
Corrosion characteristics	Not corrosive to the container material.
Explodability	The product does not contain explosive materials.

1.3 Directions for Use

1.3.1 Pyroxasulfone 85 WG Herbicide

Pyroxasulfone 85 WG, containing pyroxasulfone at 85%, is a selective herbicide for control of barnyard grass, giant foxtail, yellow foxtail, green foxtail, large crabgrass, Italian ryegrass, redroot pigweed, and common waterhemp in all types of field corn. Pyroxasulfone 85 WG can be used as a pre-plant surface treatment, a pre-emergence treatment or an early post-emergence treatment in field corn. The product is to be applied once per growing season in the spring at rates from 123 to 247 g a.i./ha (equivalent to 145 to 290 g/ha) (Table 1.3.1) with ground application equipment only.

Table 1.3.1 Application rates and weed control claims for Pyroxasulfone 85 WG

Soil textures	Rate (g a.i./ha)	Weeds Controlled
Coarse	123 (145 g/ha)	Control of barnyard grass, giant foxtail, yellow foxtail, green foxtail, large crabgrass, Italian ryegrass, redroot pigweed, and common waterhemp.
Medium to medium-fine (OM content ≤ 3%)	166 (195 g/ha)	
Medium to medium-fine (OM content > 3%)	208 (245 g/ha)	
Fine	247 (290 g/ha)	

Pyroxasulfone 85 WG may be tank mixed with either atrazine or glyphosate (present as isopropylamine salt, diammonium salt, or potassium salt) to broaden the spectrum of weeds controlled or for faster burndown (refer to the atrazine and glyphosate herbicide labels for application rates and weed species controlled) (Table 1.3.2).

Table 1.3.2 Application rates and weed control claims for Pyroxasulfone 85 WG in tank mixture with either atrazine or glyphosate herbicide

Products	Rates	Weed and crop claims
Pyroxasulfone 85 WG plus Aatrex 90 WG or Aatrex Liquid 480 or Atrazine 500	145 – 290 g/ha 1.1 – 1.7 kg/ha 2.1 – 3.1 L/ha 2.0 – 3.0 L/ha	Control of weeds listed on Pyroxasulfone 85 WG and atrazine labels. For use in field corn as pre-plant surface, pre-emergence, and early post-emergence treatments.
Pyroxasulfone 85 WG plus glyphosate products (present as isopropylamine, potassium, or diammonium salt)	145 – 290 g/ha Refer to the glyphosate label	Control of weeds listed on Pyroxasulfone 85 WG and glyphosate labels. For use in field corn as pre-plant surface and pre-emergence treatments.

1.4 Mode of Action

Pyroxasulfone is a novel pre-emergence herbicide discovered amongst a series of herbicidal 3-sulfonylisoxazoline derivatives. Pyroxasulfone inhibits very-long-chain fatty acid (VLCFA) synthesis by interfering with elongation of the C18 chains, which are normally catalyzed by VLCFA elongases. This causes inhibition of shoot elongation after seed germination. Formation of cell membranes and waxy cuticle materials within developing plant tissue is also severely affected by lack of VLCFAs. The active ingredient of pyroxasulfone enters target plants through root-uptake or via the apical meristem. This compound is primarily efficacious against annual grasses and also provides control of certain broadleaf weeds.

Pyroxasulfone is regarded as a Weed Science Society of America Group 15 Herbicide or Herbicide Resistance Action Committee Group K3 Herbicide.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Pyroxasulfone Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis in Soil and Water

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

2.4 Methods for Residue Analysis in Plant and Animal Commodities

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods were developed and proposed for data gathering and enforcement purposes in plant and livestock commodities. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled plant samples from the metabolism studies. Methods for residue analysis are summarized in Appendix I, Table 2.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for pyroxasulfone was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of toxic effects that may result from exposure to pyroxasulfone.

Pyroxasulfone technical was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits. Pyroxasulfone was not considered to be a dermal sensitizer according to the local lymph node assay test method.

The end-use product Pyroxasulfone 85 WG was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats, and was minimally irritating to the skin and eyes of rabbits. It was a dermal sensitizer in guinea pigs according to the Buehler test method.

Metabolism studies with radiolabelled pyroxasulfone were performed on rats, mice and dogs. In rats, pyroxasulfone was rapidly absorbed, extensively metabolized, and excreted primarily in the urine except following a single oral high dose, which resulted in predominantly fecal excretion. Pyroxasulfone was rapidly and widely distributed in the body. The highest radioactive residues, other than gastrointestinal tract, were observed in the kidney, blood (red blood cells), liver, heart, lungs, spleen. Total radioactivity remaining in the carcass was low at 96 hours post-dosing; there was no evidence of bioaccumulation. The main metabolic pathways involved cleavage of the sulfonyl group and subsequent sequential oxidations on the pyrazole moiety, or glutathione conjugation and hydrolysis of the isoxazoline moiety. A secondary pathway involved sequential oxidations of the parent compound. The majority of the urinary metabolites were produced by cleavage of the bond between the pyrazole and isoxazoline rings. The major metabolites found in bile were glucuronide and/or sulfate conjugates of hydroxy-pyroxasulfone. The parent compound was predominant in the feces. There were no apparent differences in the metabolism and disposition of pyroxasulfone between the sexes, or following single and repeated exposures.

In female mice, the highest concentrations of the radiolabel were seen in the excretory organs, liver and gallbladder. Pyroxasulfone was extensively metabolized in mice and produced a similar urinary metabolic profile as rats. Excretion occurred primarily through the urine.

In female dogs, the radiolabel was widely distributed in the blood, heart, liver and kidney. Metabolism occurred at the methyl group of the isoxazole ring, the sulfur atom and the N-methyl group in the pyrazole ring. In contrast to rodents, the radiolabel was excreted in similar proportions in the urine and feces of dogs.

After 28 days of dermal dosing in rats, treatment-related myofiber degeneration in the heart and treated skin were observed at the limit dose. Other effects included mucosal inflammation in the cecum and perivascular inflammation in the lungs of males.

A 28-day inhalation toxicity study in rats did not reveal any treatment-related effects up to 200 mg/m^3/day of pyroxasulfone dust (approximately 40.78/50.49 mg/kg bw/day M/F).

After repeated oral dosing in rats, the primary target organs were the liver, heart, skeletal muscle, urinary bladder and sciatic nerves. In short-term studies, the principal liver effects were increased organ weights associated with hepatocellular vacuolation and/or hypertrophy, reflecting an adaptive response to treatment with pyroxasulfone. Degeneration/necrosis of the myofibers of the heart and/or skeletal muscle (quadriceps, sternal muscle and diaphragm) was also observed at high dose levels. A supplemental 28-day dietary study in rats at similar dose levels demonstrated that myocardial necrosis/degeneration occurred as early as 8 days post-dosing in females. In a 90-day rat study, the effects on the heart and muscle resolved by the end of a 4-week recovery period. Following 1 or 2 years of dosing, the only cardiac effect was an increased incidence and severity of cardiomyopathy. Treatment-related mucosal hyperplasia in the urinary bladder of male rats occurred after 90 days of treatment. In addition to this finding, increased incidences of red discharge from the penis, red-stained cage boards and mucosal inflammation in the urinary bladder were observed following long-term dosing in males. Female rats exhibited an increased incidence of sciatic nerve degeneration after 2 years of pyroxasulfone treatment.

Following repeated oral dosing in mice, the primary target organs of toxicity were the liver, kidney and sciatic nerves. In short-term studies, treatment-related liver effects consisted of increased organ weights associated with hepatocellular vacuolation and/or hypertrophy. Treatment-related chronic progressive nephropathy was observed in female mice after 90 days of pyroxasulfone treatment. Increased incidences of retrograde nephropathy, intratubular precipitate and tubular hyperplasia were observed predominantly in male mice following 18 months of dosing. Treatment-related axonal and myelin degeneration of the sciatic and trigeminal nerves, with extension into the dorsal funiculi of the spinal cord, were observed in both sexes after long-term dosing with pyroxasulfone.

In dogs, the target organs of toxicity after repeated oral dosing were the sciatic nerves and skeletal muscle. In a short-term study, one male exhibited increased muscle fibre degeneration in the diaphragm, diffuse hyperplasia of the satellite cells of the muscle and nerve fibre degeneration in sciatic nerves at low dose levels (10 mg/kg bw/day). A subsequent 90-day study was conducted at a slightly higher dose level (15 mg/kg bw/day) to clarify the toxicity of pyroxasulfone on peripheral nerves and muscle tissue. In this study, treatment-related neurotoxic clinical signs (for example, abnormal limb function, decreased muscle tone, abnormal gait, decreased limb grip strength) were observed in 1-2 males starting at week 11. Histopathological examinations revealed increased incidences of sciatic nerve axonal/myelin degeneration, as well as subacute inflammation and/or myofiber degeneration in skeletal muscle (diaphragm, superficial digital flexor, biceps femoris). These findings suggest a steep dose-response relationship for peripheral nerve and skeletal muscle toxicity after short-term dosing with pyroxasulfone. Following 12 months of dosing, similar clinical signs were noted in 3 males and

2 females at low dose levels (10 mg/kg bw/day). Slight impairment of limb grip strength was observed in individual dogs as early as weeks 7-9. More serious neurotoxic effects, including clonic movements, slow papillary response and circling, were observed sporadically throughout the study period. At necropsy, sciatic nerve and spinal cord degeneration were seen in almost all of the high dose animals and were associated with skeletal muscle degeneration/necrosis in select males.

Durational effects of dosing were observed with pyroxasulfone treatment across all tested species. Rats and dogs were more sensitive to pyroxasulfone-induced toxicity than mice.

Pyroxasulfone was not genotoxic in a standard battery of *in vitro* and *in vivo* assays, and did not cause immunosuppression in mice or rats.

With respect to oncogenicity, statistically identified incidences of renal tubular adenomas were seen in male mouse kidneys at 131.3 mg/kg bw/day (incidences 0, 1, 0, 3 at 0, 0.61, 18.6, 131.3 mg/kg bw/day respectively). A re-evaluation of the histological data by an expert renal pathologist provided strong evidence that the tumours were unrelated to treatment and that the observation of tubular nephrosis previously identified by the study pathologist was actually mis-classified and represented a retrograde nephropathy (PMRA #2052929). This condition is not known to be associated with renal tubular neoplasia. A re-assessment of the slides from all of the mouse toxicity studies did not demonstrate any tubule cell degeneration/necrosis or cells with high mitotic indices. The expert pathologist stated that most of the proliferative lesions reported as hyperplasias in the original study report appeared to be represented by dilated proximal tubules with simple hyperplasic lining, which is not a precursor for renal tubule neoplasia. Based on this and the sporadic pattern of renal tubular adenomas noted in the 18-month study, the low incidence of benign renal tumours in male mice at 131.3 mg/kg bw/day were not considered to be treatment-related.

An increased incidence of urinary bladder transitional cell papillomas was observed in male rats at 1000 ppm (42.6 mg/kg bw/day) and 2000 ppm (84.6 mg/kg bw/day) relative to concurrent controls after 99 weeks of treatment with pyroxasulfone. The incidences were 1, 0, 0, 4, 5 at 0, 0.21, 2.1, 42.6, 84.6 mg/kg bw/day respectively. The increases were not statistically significant and were slightly outside of the testing laboratory's historical control values. The applicant proposed an association between site-specific cytotoxicity secondary to crystals/calculi, chronic irritation and spontaneous neoplastic initiation in bladder cells (resulting from a compensatory regenerative hyperplastic response) as contributing factors for the bladder tumours. Although calculi were not consistently seen in all of the rat toxicity studies, crystals and/or urothelial erosion (craters) were seen as early as 1-3 days after treatment with pyroxasulfone at ≥50 ppm. The presence of calculi in the bladder is dependent upon the size of the crystals, the urinary volume and the concentration of the solutes over time (PMRA #2041483). This key event was associated with evidence of cytotoxicity (chronic inflammation and morphologic changes to the bladder epithelium) and cell proliferation (hyperplasia, BrdU labeling) at doses where tumours were seen in the long-term study. The toxicity studies in rats showed a progression of increasing bladder toxicity with a relationship to dose level and time. All tumour-bearing males presented with non-neoplastic lesions such as mucosal hyperplasia and inflammation. Overall, the results indicated that the proposed key events (i.e. crystal formation, cytotoxicity, regenerative proliferation and papillomas) generally occurred in a dose- and time-dependent manner. For these reasons, the threshold-based mechanism for tumour formation was accepted by the PMRA.

In a 2-generation reproductive toxicity study, treatment-related effects in the parental animals consisted of decreased body weight/gains, reduced food consumption, cardiomyopathy (females only), sciatic nerve degeneration (F_0 generation females only), and mucosal inflammation and/or hyperplasia of the urinary bladders at the high dose level. There was no evidence of reproductive toxicity. Decreased pup body weights at birth and throughout lactation were noted at the highest dose tested. Although treatment-related, these effects were marginal and occurred at maternally toxic doses. Consequently, they were considered to be of low toxicological concern.

In a rat developmental toxicity study, no maternal or developmental toxicity (including teratogenicity) was observed up to and including the limit dose. In a rabbit developmental toxicity study, no maternal toxicity was observed up to the limit dose. There was no evidence of teratogenicity in rabbits; however, decreased fetal weights and increased early and total resorptions per doe were noted at the limit dose. The latter finding could not be specifically attributed to maternal or developmental toxicity, and was not considered to represent a fetal sensitivity.

Pyroxasulfone was not neurotoxic in an acute neurotoxicity study in rats. However, in a rat subchronic neurotoxicity study, one high dose female showed mild myofiber degeneration in the gastrocnemius muscle. Based on the neurotoxicological effects observed in other pyroxasulfone toxicity studies, this singular incidence was considered to be treatment-related. In a rat developmental neurotoxicity (DNT) study, there was no evidence of maternal toxicity. Treatment-related decreased absolute and relative brain weights and decreased thicknesses of the hippocampus, corpus callosum and pyramis folia of the cerebellum were observed in postnatal day (PND) 21 female offspring at doses greater than or equal to 300 mg/kg bw/day. Decreased brain weights and decreased hippocampus thickness were seen in the PND 66 females of the high dose group.

Studies conducted with select metabolites (M-1, M-3, M-25, M-28) and impurities (I-3, I-4, I-5) of pyroxasulfone indicated that they were of low acute oral toxicity and were not genotoxic in bacteria. After short-term oral dosing with M-1 or M-3, there were no treatment-related effects up to the limit dose in rats. The results suggest that these metabolites and impurities are not more toxic than pyroxasulfone.

Results of the acute and repeat dose tests conducted on laboratory animals with pyroxasulfone technical and its associated end-use product, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 3, 4, and 5 of Appendix I.

3.1.1 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched and reviewed for pyroxasulfone. As of May 2011, there were no health-related incident reports submitted to the PMRA, or in the United States, for end use products containing pyroxasulfone.

3.1.2 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including developmental toxicity studies in rats and rabbits, as well as rat reproductive toxicity and developmental neurotoxicity studies.

With respect to identified concerns relevant to the assessment of risk to infants and children, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and rat developmental toxicity studies. No treatment-related effects were noted in the rat developmental toxicity study. In the rat reproduction study, decreased pup body weights were observed at birth and throughout lactation in the presence of maternal toxicity. Decreased fetal weights and increased incidences of early and total resorptions per doe were observed in the rabbit developmental toxicity study; however, these effects occurred at the limit dose. The latter finding could not be specifically attributed to maternal or developmental toxicity, and was not considered to represent a fetal sensitivity. Serious endpoints (decreased brain weights and brain morphometric measurements) were observed in the PND 21 female offspring in the rat DNT study in the absence of adverse effects on the maternal animals. On the basis of this information, the full 10-fold factor required under the *Pest Control Products Act* was not reduced for scenarios for which this endpoint was relevant. For all other scenarios, the PCPA factor was reduced to 1-fold since there were no residual uncertainties with respect to the completeness of the data, or with respect to potential toxicity to infants and children.

3.2 Acute Reference Dose (ARfD)

General Population

To estimate acute dietary risk (1 day), the rat developmental neurotoxicity study with a neurotoxicity NOAEL of 100 mg/kg bw/day was selected for risk assessment. The lowest observed adverse effect level (LOAEL) of 300 mg/kg bw/day was based on decreased absolute and relative brain weights, and reduced thickness of the hippocampus, corpus callosum and cerebellum in female offspring on PND 21. These effects were considered to result from a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the PCPA Hazard Characterization Section, the full PCPA factor was retained at 10-fold. **The composite assessment factor (CAF) of 1000-fold.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw}}{1000} = 0.10 \text{ mg/kg bw of pyroxasulfone}$$

The ARfD provides a margin of 5000 to the NOAEL for developmental toxicity in the rabbit and is thus considered protective of pregnant women and their fetuses.

3.3 Acceptable Daily Intake (ADI)

To estimate dietary risk of repeat exposure, the 12-month dog toxicity study with a NOAEL of 2.0 mg/kg bw/day was selected for risk assessment. At the LOAEL of 10 mg/kg bw/day, impaired hindlimb function and other neurotoxic effects, clinical pathology, and axonal/myelin degeneration of the sciatic nerve and spinal cord were observed. This endpoint is supported by the NOAEL of 2.0 mg/kg bw/day from the 2-year rat carcinogenicity study. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. The NOAEL in the 1-year dog oral toxicity study selected for the ADI is considered to be protective of the effects observed in the rat developmental neurotoxicity study. For this reason, it was considered appropriate to reduce the PCPA factor from 10-fold to 1-fold. **Therefore, the composite assessment factor is 100-fold.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{2.0 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day of pyroxasulfone}$$

This ADI provides margins of 2128 to the dose at which urinary bladder tumours were noted in male rats and 15,000 to the dose where decreased brain weights and brain morphometric measurements were observed in rat offspring.

Cancer Assessment

There was adequate evidence to support a threshold-based mode of action for the urinary bladder transitional cell papillomas in male rats. The dietary reference dose (i.e. the ADI) and the target MOEs for occupational and bystander exposure provide a sufficient margin to this tumour.

3.4 Occupational Risk Assessment

3.4.1 Toxicological Endpoints

Short-term dermal and inhalation

Separate route-specific short-term dermal and inhalation toxicity studies are available in rats; however, the studies are not designed to assess a critical endpoint for the risk assessment, namely brain morphometry in offspring. Although a 90-day dog study produced a lower NOAEL than the DNT study, the effects observed occurred in only one dog and the duration of the DNT study was considered to be more appropriate for these scenarios. Therefore, the NOAEL of 100 mg/kg bw/day in the rat DNT study was selected. The NOAEL is based on decreased brain weights and decreased brain morphometrics (corpus callosum, cerebellum) in PND 21 female offspring at the LOAEL of 300 mg/kg bw/day. An additional factor of 10-fold was applied on the basis of the concerns identified in the PCPA Hazard Characterization section. Therefore, the target margin of exposure (MOE) is 1000. The selection of this study and target MOE is considered to be protective of all populations including nursing infants and the unborn children of exposed female workers.

Intermediate-term dermal and inhalation

Separate route-specific short-term dermal and inhalation toxicity studies are available in rats; however, longer duration dermal or inhalation toxicity studies are not available, and rats and dogs exhibited more serious effects after longer term oral administration of pyroxasulfone and at lower effect levels. Therefore, the oral 12-month dog toxicity study NOAEL of 2 mg/kg bw/day was considered to be the most appropriate endpoint. The NOAEL is based on neurotoxic clinical signs, clinical pathology, and axonal/myelin degeneration of sciatic nerve and spinal cord at the LOAEL of 10 mg/kg bw/day. This endpoint is considered to be protective of the effects observed in the rat developmental neurotoxicity study. For this reason, an additional factor was not required. Therefore, the target MOE is 100. The selection of this endpoint and target MOE is considered protective of all populations including women of child-bearing age and nursing infants.

Occupational exposure to pyroxasulfone is characterized as being of short-term duration and is predominantly by the dermal and inhalation route for chemical handlers and by the dermal route for workers re-entering treated areas.

3.4.1.1 Dermal Absorption

A chemical-specific dermal absorption study for pyroxasulfone was not submitted. A weight-of-evidence approach was considered to refine the dermal absorption value. Pyroxasulfone has a molecular weight of 391.3 amu, which indicates that that it might have high absorption potential. In addition, it has a log P_{ow} of 2.39, which falls within the optimal range for high dermal absorption potential. The trifluromethyl (CF_3-) and difluromethoxy (CHF_2-O-) groups enhance the liposolubility of pyroxasulfone. As such, the dermal absorption cannot be refined using a weight-of-evidence approach and a dermal absorption value of 100% was used for pyroxasulfone for risk assessment purposes.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Individuals have potential for exposure to Pyroxasulfone 85 WG during mixing, loading and application. Exposure to workers mixing, loading and applying Pyroxasulfone 85 WG is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders and applicators applying Pyroxasulfone 85 WG to field corn using groundboom sprayers.

For Pyroxasulfone 85WG, the exposure estimates are based on mixer/loaders and applicators with the following PPE and engineering controls:

- When handling 41 kg of product or less per day:
  - Wear a long-sleeved shirt and long pants (and chemical-resistant gloves during mixing/loading)
- When handling more than 41 kg of product per day:
  - Wear chemical-resistant coveralls over a single layer and chemical-resistant gloves during mixing/loading and wear coveralls over a single layer during application, and apply in a closed cab tractor

As chemical-specific data for assessing human exposures were not submitted, dermal and inhalation exposures for workers were estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the default 100% dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoint (no observable adverse effect limit [NOAEL] = 100 mg/kg bw/day) to obtain the margin of exposures (MOEs); the target MOE is 1000. Tables 1 and 2 below present the PHED unit exposure values and estimates of exposure and risk, respectively, for Pyroxasulfone 85 WG. Acceptable MOEs were calculated for workers who wear the PPE, use the engineering controls, and follow the directions on the product label.

Table 1 PHED unit exposure estimates for mixer/loader and applicators while handling Pyroxasulfone 85WG (µg/kg ai handled)

Scenario		Dermal*	Inhalation	Total unit exposure (dermal + inhalation)
Mixer/loader PHED estimates (Dry Flowable)				
A	Open mixing/loading (single layer and gloves)	163.77	1.02	164.79
B	Open mixing/loading (chemical resistant coveralls, single layer and gloves)	77.57	1.02	78.59
Applicator PHED estimates				
C	Groundboom open cab (single layer, no gloves)	32.98	0.96	33.94
D	Groundboom closed cab (cotton coveralls over single layer, no gloves)	4.42	0.06	4.48
Mixer/loader and applicator PHED estimates				
A+C	Open mixing/loading (single layer and gloves) and groundboom open cab (single layer, no gloves)	196.75	1.98	198.73
B+D	Open mixing/loading (chemical-resistant coveralls over single layer and gloves) and groundboom closed cab (cotton coveralls, single layer, no gloves)	81.99	1.08	83.07

* Dermal unit exposure was not adjusted since the default dermal absorption value of 100% was used.

Table 2 Chemical handler risk assessment for Pyroxasulfone 85WG

Scenario	PHED unit exposure (µg/kg ai handled)	ATPD[1] (ha/day)	Rate (kg ai/ha)	Daily exposure[2] (mg/kg bw/day)	MOE[3] (target MOE=1000)
Single layer with gloves when open mixing/loading, single layer when applying in open cab					
Farmer	198.73	107	0.247	0.0749	1335
Custom	198.73	360	0.247	0.252	**397**
Custom	198.73	141*	0.247	0.0987	1013
Max PPE and closed cab: Chemical resistant coveralls over single layer with gloves when open mixing/loading, and cloth coveralls over single layer with gloves when applying in closed cab					
Custom	83.07	360	0.247	0.105	**950†**

[1] Default area treated per day (ATPD) values

[2] Daily exposure = [Total unit exposure (µg/kg ai handled) × Area Treated Per Day (ha/day) × Rate (kg ai/ha)] / [70 kg bw × 1000 µg/mg]

[3] NOAEL = 100 mg/kg bw/day, target MOE = 1000

Bolded MOEs are below the target MOE of 1000.

* Restricted to handling 41 kg of product per day (34.85 kg ai/day)

† Although the calculated MOE is below the target MOE of 1000, taking into account the conservativisms of the risk assessment, such as assuming 100% dermal absorption, the estimated risk for custom applicators is considered acceptable.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Pre-plant or pre-emergence use of Pyroxasulfone 85 WG Herbicide would have no associated postapplication exposure potential. However, postapplication dermal exposure may occur during scouting activities after early post-emergence use. The duration of exposure is considered to be short-term.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients. Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value (DFR) of 20% of the application rate was used in the exposure assessment.

The exposure estimate was compared to the toxicological endpoint (NOAEL = 100 mg/kg bw/day) to obtain the MOE; the target MOE is 1000. Since this value exceeds the target MOE of 1000 (see Table 3 below), this level of postapplication exposure is not a health concern. The proposed 12-hour REI is adequate to protect re-entry workers.

Table 3 Postapplication exposure and risk estimate for re-entering field corn treated with Pyroxasulfone 85 WG (early post-emergence)

Re-entry activity	Peak DFR (µg/cm^2)[1]	Transfer Coefficient (cm^2/hr)[2]	Dermal Exposure (mg/kg bw/day)[3]	MOE[4]	REI [5]
Scouting	0.494	400	0.023	4400	12 hours

[1] Calculated using the default 20% of the application rate dislodgeable on the day of application

[2] Transfer coefficients (TCs) obtained from EPA Policy 3.1

[3] Exposure = (Peak DFR [µg/cm^2] × TC [cm^2/hr] × 8 hours x 100% dermal absorption) / (70 kg bw × 1000 µg/mg).

[4] NOAEL = 100 mg/kg bw/day, target MOE = 1000

[5] Minimum REI is 12 hours to allow residues to dry.

3.4.3 Residential Exposure and Risk Assessment

There are no residential uses for Pyroxasulfone 85 WG and as such, as residential risk assessment was not required.

3.4.3.1 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition is pyroxasulfone and the metabolite M3 for both enforcement and risk assessment purposes in plant commodities. The residue definition is pyroxasulfone for both enforcement and risk assessment purposes in livestock commodities. The LC-MS/MS enforcement analytical method (Report# 1518W) is valid for the quantitation of pyroxasulfone and M3 residues in plant matrices. The LC-MS/MS enforcement analytical method (Report# 1745W) is valid for the quantitation of pyroxasulfone residues in livestock matrices. The freezer storage stability data for pyroxasulfone and M3 residues cover the longest storage period in the field trials and processing studies for corn. Pyroxasulfone residues do not concentrate in field corn processed commodities. The anticipated pyroxasulfone residues are <0.01 ppm in eggs, fat, meat, meat by-products of cattle, goats, hogs, horses, poultry and sheep, and <0.001 ppm in milk. Supervised residue trials conducted throughout the United States using the end-use product containing pyroxasulfone at the supported rates in/on field corn and sweet corn are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

For the chronic dietary exposure assessment, the highest pyroxasulfone combined residues for all domestic and imported crops and the MRL-level livestock commodities were used. It was assumed that 100% of the crops were treated. The basic chronic dietary exposure from all supported pyroxasulfone food uses (alone) for the general population, including infants and children, and all representative population subgroups is ≤0.8% of the acceptable daily intake. Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to pyroxasulfone from food and water is 28.6% (0.005711 mg/kg bw/day) of the ADI for the general population. The highest exposure and risk estimate is for all infants (<1 year old) at 92.9% (0.018589 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The basic acute dietary exposure (food alone) from all supported pyroxasulfone food uses is estimated to be 0.17% (0.000167 mg/kg bw/day) of the ARfD for the general population (95th percentile, deterministic). Aggregate exposure from food and water is considered acceptable at 14.2% of the ARfD (0.014197 mg/kg bw/day) for the general population (95th percentile, deterministic). The highest exposure and risk estimate is for all infants (<1 year old) at 53.1% (0.053143 mg/kg bw/day) of the ARfD (95th percentile, deterministic).

3.5.3 Aggregate Exposure and Risk

The aggregate risk for pyroxasulfone consists of exposure from food and drinking water sources only. Aggregate risks were calculated based on acute and chronic endpoints.

3.5.4 Maximum Residue Limits

Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Field corn	0.015
Popcorn grain	0.015
Sweet corn kernels plus cob with husks removed	0.015
Eggs	0.01
Fat, meat and meat by-products of cattle, goats, hogs, horses, poultry, and sheep	0.01
Milk	0.001

For additional information on Maximum Residue Limits (MRL) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Tables 2, 6 and 7 in Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The physical and chemical characteristics of pyroxasulfone are summarized in Appendix I, Table 8. The maximum formation in the environment and the chemical structures of transformation products can be found in Table 9. The environmental fate data for pyroxasulfone are summarized in Appendix I, Table 10.

Pyroxasulfone technical has low solubility in water, is not expected to volatilize under field conditions, does not have a dissociable moiety, and is not expected to phototransform in the environment (Table 8 in Appendix I).

Pyroxasulfone and the major transformation product, KIH-485-M-1, are moderately persistent to persistent in soil under both aerobic and anaerobic conditions in the laboratory. The transformation product KIH-485-M-1 is more persistent than the parent in laboratory soil studies. Terrestrial field studies, however, indicated that KIH-485 and KIH-485-M-1 would be less persistent under conditions of use. KIH-485-M-1 was measured in the field study in low concentrations in the first 15 cm of soil only and dissipated faster than it transformed in laboratory studies. It was not detected after 6 months.

Another transformation product, KIH-485-M-3, was also monitored but barely detected in the terrestrial field dissipation study. It was, however, found in anaerobic soil at levels only slightly > 10% applied radioactivity (AR) in the whole test system (10.2%AR at study termination;4.0 and 6.3 %AR in soil and water compartments, respectively).

Laboratory mobility studies indicate that pyroxasulfone and the major transformation product, KIH-485-M-1, have high to medium mobility, with KIH-485-M-1 being more mobile. Based on this information, the groundwater ubiquity score (GUS), laboratory biotransformation studies, and results from field studies, the potential for leaching in different soil types was assessed. Leaching through soil is likely to be a major route of dissipation of pyroxasulfone and its major transformation product, KIH-485-M-1, in the environment, regardless of soil type. This is supported by the slow rates of biotransformation of these substances in soil under laboratory conditions, lack of importance of abiotic transformation processes, and the apparent quick dissipation of pyroxasulfone from a flooded field (dissipation from the flooded field was faster than in the terrestrial field study), most likely due to leaching.

In aquatic systems, abiotic routes of transformation of pyroxasulfone are not likely to be important. Although pyroxasulfone did biotransform in aquatic conditions, it is considered to be moderately persistent to persistent.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints (for example, LC_{50}, LD_{50}, and EC_{50}) used in risk assessments may be multiplied by an uncertainty factor to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated. The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (i.e. feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. When assessing chronic risk, the NOEC or NOEL is used and an uncertainty factor is not applied.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints.

A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A summary of the toxicity data of KIH-485 to terrestrial non-target organisms can be found in Table 11 of Appendix I.

Invertebrates

Earthworms
The screening level EECs for pyroxasulfone for a direct over-spray application at the maximum rate of Pyroxasulfone 85WG (85% pyroxasulfone; application of 290 g product/ha, equivalent to 247 g a.i./ha) soil assuming soil bulk density of 1.5 g/cm3 is 0.1098 mg a.i./kg for soil depths of 15 cm. Exposure to Pyroxasulfone 85WG is not expected to pose a risk to earthworms (Table 12, Appendix I).

Arthropods
The risk to non-target terrestrial invertebrates was assessed using the Pyroxasulfone 85WG application rate (247 g a.i./ha) for the screening assessment. Pyroxasulfone 85WG is not expected to pose a risk to non-target terrestrial invertebrates (honeybees, predatory mites and parasitoid wasps; Table 12, Appendix I).

Birds and mammals
The EECs on food items (vegetation and insects) can be found in Table 13 of Appendix I.

Wild mammals seemed somewhat more sensitive (reproduction) than birds to the active ingredient when exposed daily for a prolonged period of time (before mating, throughout gestation and during lactation) to the maximum potential residue level. However, the likelihood of these effects occurring following the highest (single) application rate of Pyroxasulfone 85WG is small considering that the birds and mammals are going to be exposed to a range of residue concentrations which are less than the assumed maximum residue concentration during the screening level risk assessment. Also, as this product is to be applied to bare ground, the risk to birds and mammals off field will be small as the spray deposition will significantly be reduced compared to the direct application on field. Therefore, exposure to food items contaminated with pyroxasulfone following the highest proposed application rate of Pyroxasulfone 85WG is expected to be acceptable for both birds and mammals (Tables 14 - 18, Appendix I).

Terrestrial plants

The EEC for terrestrial plants assumes direct application of Pyroxasulfone 85WG at the maximum application rate of 290 g product/ha, equivalent to 247 g a.i./ha.

As only a few plant species showed adverse effects and the EC_{50} could not be calculated in both the seedling emergence and vegetative vigour studies, conducting a probalistic assessment (HC_5 of the EC_{50}s) was not required for terrestrial plants. As such, the most sensitive endpoint was chosen for the terrestrial plant risk assessment. The onion seedling emergence study (EC_{25} = 75 g a.i./ha) was assessed and showed negligible risk (Table 19, Appendix I).

4.2.2 Risks to Aquatic Organisms

A summary of the toxicity data of pyroxasulfone to aquatic non-target organisms can be found in Table 20, Appendix I.

The screening level EECs in surface water are calculated assuming an application of the full rate of Pyroxasulfone 85WG (85% pyroxasulfone; application of 290 g product/ha, equivalent to 247 g a.i./ha) with water depths of 15 cm for a temporary (seasonal) water body and 80 cm for a permanent water body. The EECS were calculated to be 0.17 and 0.031 mg a.i./L, for depths of 15 cm and 80 cm, respectively. Table 22 shows the runoff EECs in water from the Level 1 ecoscenario water modelling.

Invertebrates and Fish

Although most of the toxicity endpoints showed moderate toxicity, the level of concern (LOC) for fish, invertebrates and molluscs, both in freshwater and marine environments was not exceeded (Table 21, Appendix I) up to the limit of solubility (3.49 mg a.i./L).

Although information on the toxicity of pyroxasulfone or KIH-485-M-1 to amphibians was not submitted, the acute freshwater fish toxicity data was used as a surrogate to assess the risk to amphibians. The EEC for amphibians was calculated using a temporary (seasonal) water body of 15 cm. As for the fish endpoint, the level of concern (LOC) was not exceeded (Table 21, Appendix I) up to the limit of solubility (3.49 mg a.i./L).

Aquatic plants

Freshwater algae (*Pseudokirchneriella subcapitata*) and vascular plants (*Lemna gibba*) are sensitive to pyroxasulfone. As the RQ's for alga (195) and Lemna (12.4) exceeded the LOC, a refined (Tier 1) analysis was conducted for both spray drift and runoff scenarios.

Spray Drift: Pyroxasulfone 85WG is proposed to be applied by ground spraying equipment. According to the American Society of Agricultural Engineering (ASAE), a ground boom sprayer with medium droplet size deposits 6% of the application rate at 1 m downwind of the spray boom. As such, the RQs for freshwater alga and for duckweed exposed through spray drift were calculated to be 12.0 and 0.7, respectively (Table 22, Appendix I). To mitigate the risk in seasonal (<1m) and permanent water bodies (>1m), buffer zones for Pyroxasulfone 85WG buffer zones were calculated to be 5 and 3 meters, respectively, based on the endpoint for algae. Marine habitats do not require buffer zones.

Runoff: Simulation models with regional agricultural scenarios were used to estimate the concentrations of pyroxasulfone due to runoff in a generic water body (Table 23, Appendix I). Risk quotients for runoff were exceeded for both algae and aquatic vascular plants, thus a precautionary label statement regarding runoff is required.

4.2.3 Incident reports

There were no incident reports for pyroxasulfone or its major transformation product.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims for Pyroxasulfone 85 WG Herbicide

Efficacy data were submitted for review from a total of 240 field trials conducted in the US and Canada during a 5 year period (2004 to 2008). A total of 65 trials were found to be not applicable due to the following reasons:

- Differences in the ecological conditions of the trial locations to Canada (26 trials in Florida, Mississippi, Texas, and Virginia);
- Appropriate treatments were not included and weeds listed on the label were not assessed (39 trials).

The remaining 175 appropriately designed and relevantly located trials were conducted in 19 states of the US and in Ontario, Canada. The trials were conducted on a wide range of soil types with organic matter content up to 6.6% and pH varying from 5.2 to 8.5. Application rates of Pyroxasulfone 85 WG ranged from 25 g a.i./ha up to 505 g a.i./ha were assessed to determine the lowest effective rate (LER). The herbicides were applied using small plot application equipment.

In a total of 151 trials, the efficacy of Pyroxasulfone 85 WG as a pre-emergence treatment, applied alone (151 trials) or in a tank mixture with atrazine (17 trials) or glyphosate (43 trials), for giant foxtail, yellow foxtail, green foxtail, Italian ryegrass, large crabgrass, barnyard grass, redroot pigweed, and common waterhemp was visually assessed and reported as a percentage (%) compared to an untreated weedy check. Observations were made up to four times throughout the growing season.

Efficacy of Pyroxasulfone 85 WG as a pre-plant incorporated treatment for giant foxtail, yellow foxtail, green foxtail, barnyard grass, and redroot pigweed was visually assessed in 4 trials and reported as a percentage (%) compared to an untreated weedy control. A pre-emergence application of Pyroxasulfone 85 WG was included in all 4 trials as a positive control.

Efficacy of Pyroxasulfone 85 WG as a pre-plant surface treatment for giant foxtail, barnyard grass, and common waterhemp was visually assessed in 10 trials and reported as a percentage (%) compared to an untreated weedy control. A pre-emergence application of Pyroxasulfone 85 WG was included in 5 trials as a positive control.

5.1.1.1 Pyroxasulfone 85 WG Herbicide Applied as an Alone Treatment

Adequate data were submitted to establish the LER for the Pyroxasulfone 85 WG treatment and to support the weed control claims that are summarized in Table 5.1.1. Use of Pyroxasulfone 85 WG is prohibited on peat or muck soils and soils with 7% or more organic matter content.

Table 5.1.1 Application rates and weed control claims for Pyroxasulfone 85 WG

Soil textures	Rate (g a.i./ha)	Weeds Controlled
Coarse	123 (145 g/ha)	Control of barnyard grass, giant foxtail, yellow foxtail, green foxtail, large crabgrass, Italian ryegrass, redroot pigweed, and common waterhemp.
Medium to medium-fine (OM content ≤ 3%)	166 (195 g/ha)	
Medium to medium-fine (OM content > 3%)	208 (245 g/ha)	
Fine	247 (290 g/ha)	

Pyroxasulfone 85 WG can be applied as a pre-emergence treatment, a pre-plant surface treatment up to 30 days before planting or as an early post-emergence treatment in field corn (but pre-emergent to weeds).

5.1.1.2 Pyroxasulfone 85 WG Herbicide Applied in a Tank Mixture With Atrazine or Glyphosate Herbicide

Adequate data were provided to support weed control claims for the herbicide tank mixture of Pyroxasulfone 85 WG with either atrazine or glyphosate and are summarized in Table 5.1.2.

Table 5.1.2 Application rates and weed control claims for Pyroxasulfone 85 WG in tank mixture with either atrazine or glyphosate herbicide

Products	Rates	Weed and crop claims
Pyroxasulfone 85 WG plus Aatrex 90 WG or Aatrex Liquid 480 or Atrazine 500	145 – 290 g/ha 1.1 – 1.7 kg/ha 2.1 – 3.1 L/ha 2.0 – 3.0 L/ha	Control of weeds listed on Pyroxasulfone 85 WG and atrazine labels. For use on corn as pre-plant surface, pre-emergence, and early post-emergence treatments.
Pyroxasulfone 85 WG plus glyphosate products (present as isopropylamine, potassium, or diammonium salt)	145 – 290 g/ha Refer to the glyphosate label	Control of weeds listed on Pyroxasulfone 85 WG and glyphosate labels. For use on corn and soybean as pre-plant surface and pre-emergence treatments.

5.2 Phytotoxicity to Host Plants

5.2.1 Pyroxasulfone 85 WG Herbicide

Crop tolerance data were submitted from a total of 119 appropriately designed and relevantly located trials were conducted in 20 states of the US and in Ontario, Canada during a 5 year period (2004 to 2008). The trials were conducted on a wide range of soil types with organic matter content up to 6.6% and pH varying from 5.2 to 8.5. Treatments of Pyroxasulfone 85 WG at the 1 x maximum rate (i.e. 247 g a.i./ha) as well as at exaggerated rates up to 2048 g a.i./ha were assessed and reviewed to determine the phytotoxicity. The herbicides were applied using small plot application equipment.

5.2.1.1 Field Corn

Data from 119 field trials were acceptable for the review of field corn crop tolerance. A total of 12 trials were conducted on coarse soil, 47 on medium to medium-fine soil with organic matter content ≤ 3%, 35 trials on medium to medium-fine soil with organic matter content > 3%, and 25 trials on fine soil. Within these trials, crop tolerance was assessed on 77 corn hybrids after a single pre-emergence application of Pyroxasulfone 85 WG at rates up to 2048 g a.i./ha.

Crop tolerance was assessed after a pre-plant surface application (14 trials) and after a pre-plant incorporated application of Pyroxasulfone 85 WG (5 trials). As the regulatory decision for the pre-emergence application of Pyroxasulfone 85 WG can be extended to the pre-plant surface and pre-plant incorporated applications, a crop tolerance evaluation of pre-plant surface and pre-plant incorporated application was not conducted.

Crop tolerance was assessed after an early post-emergence application of Pyroxasulfone 85 WG in 5 trials. At the time of herbicide application, corn growth stage ranged from the 2 to 5 leaf stage.

The tolerance of field corn to a pre-emergence application of Pyroxasulfone 85 WG in a tank mixture with atrazine (14 trials) and glyphosate (6 trials) was assessed. In the 6 glyphosate trials, various glyphosate end use products, including Roundup Original, Roundup PowerMax (registered in the US only), Roundup WeatherMax, Touchdown iQ, and Touchdown Total, were used in the tank mix treatments and applied at rates according to their respective labels.

5.2.1.1.1 Supported Claims

Crop injury and grain yield data support a crop tolerance claim for use on field corn with either a single pre-emergence application or an early post-emergence application of Pyroxasulfone 85 WG at 123 g a.i./ha on coarse soil, 166 g a.i./ha on medium to medium-fine soil with organic matter content ≤ 3%, 208 g a.i./ha on medium to medium-fine soil with organic matter content > 3%, and 247 g a.i./ha on fine soil. The regulatory decision for pre-emergence application on field corn is also applicable to pre-plant surface and pre-plant incorporated applications.

Data from field research trials also demonstrated that field corn is tolerant to pre-emergence and early post-emergence applications of the tank mixture of Pyroxasulfone 85 WG with atrazine at 1000 to 1500 g a.i./ha and to pre-emergence applications of the tank mixture of Pyroxasulfone 85 WG with glyphosate (present as isopropylamine, potassium, or diammonium salt) at the labelled rates.

5.3 Impact on succeeding Crops

5.3.1 Pyroxasulfone 85 WG Herbicide

Data from field research trials were not submitted to support rotational crop label claims. As tolerance of field corn as primary host crop to pre-plant surface and pre-emergence application of Pyroxasulfone 85 WG was demonstrated, field corn can also be supported as immediate plant back crops if any crop treated with Pyroxasulfone 85 WG is lost.

A scientific rationale based on soil dissipation studies was provided by the applicant to support field corn as a rotational crop to be planted in the year following Pyroxasulfone 85 WG application. Field corn are acceptable to appear on the label as a rotational crop to be planted in the following year for the following reasons:

- Field corn are the primary labelled crops;
- DT_{50} of pyroxasulfone in 4 US soils ranged from 4 to 35 days and DT_{90} of pyroxasulfone ranged from 40 to 115 days;
- Concentration of the major transformation products of pyroxasulfone were below the LOQ (<0.002 to 0.006 ppm up to 12 months).

For any crop other than field corn to be planted as rotational crop in the year following an application of Pyroxasulfone 85 WG, a successful bioassay should be conducted prior to adoption as general field practice.

5.4 Economics

An economic analysis was not conducted.

5.5 Sustainability

5.5.1 Survey of Alternatives

5.5.1.1 Pyroxasulfone 85 WG Herbicide

A number of pre-emergence herbicides that control annual grasses and broadleaf weeds in field corn have been registered in Canada (see Table 5.5.1 below). The availability of Pyroxasulfone 85 WG provides another very-long-chain fatty acid (VLCFA) inhibitor herbicide (Group 15) for pre-emergence treatment in field corn. Like other Group 15 herbicides, Pyroxasulfone 85 WG not only controls annual grasses, but also has broadleaf weed activity.

Table 5.5.1 Alternative Pre-emergence Herbicides for Grass and Broadleaf Weed Control in Corn and Soybeans

TGAI	EP	Weed and Host (i.e. corn) Claims	Herbicide Classification	
			Group	Mode of Action
s-metolachlor	Dual II Magnum	Control of annual grasses, crabgrass, nightshade, yellow nutsedge, and redroot pigweed on field corn.	15	Inhibition of cell division (VLCFA inhibition)
Dimethenamid	Frontier	Control of annual grasses, redroot pigweed, black nightshade, and yellow nutsedge on field corn.	15	Inhibition of cell division (VLCFA inhibition)
Flufenacet	Flufenacet	Control / suppression of green foxtail, redroot pigweed, and lamb's-quarters in field corn.	15	Inhibition of cell division (VLCFA inhibition)
Pendimethalin	Prowl 60	Control of annual grasses and lamb's-quarters and redroot pigweed on field corn.	3	Microtubule assembly inhibition
Atrazine	Aatrex 480	Control of Broadleaf weeds and wild oats in field corn.	5	Inhibition of photosynthesis
Simazine	Simanex 80	Control of grasses and broadleaf weeds in field corn.	5	Inhibition of photosynthesis
Linuron	Lorox DF	Control of annual grass and broadleaf weeds in field corn.	7	Inhibition of photosynthesis
Isoxaflutole	Converge Flexx	Control of annual broadleaf weeds, green foxtail, and barnyard grass in field corn.	27	Inhibition of HPPD

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

A single application of Pyroxasulfone 85 WG offers pre-plant surface, pre-emergence, and early post-emergence control of annual grasses and certain broad-leaved weeds in field corn. It is compatible with integrated weed management practices and with both conservation tillage and conventional tillage systems.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Repeated use of herbicides having the same mode of action in a weed control program increases the probability of selecting naturally resistant biotypes. Therefore, Pyroxasulfone 85 WG should be used in rotation with herbicides having different modes of action.

Pyroxasulfone 85 WG provides an alternative for corn growers to Group 2, Group 3, Group 5 and Group 27 chemistries.

The Pyroxasulfone 85 WG label include the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, Pyroxasulfone and its transformation product, KIH-485-M-1, were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

Pyroxasulfone does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 24 in Appendix I for comparison with Track 1 criteria.

Pyroxasulfone does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[7] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[8] DIR2006-02, *PMRA Formulants Policy.*

- Technical grade Pyroxasulfone and the end-use product Pyroxasulfone 85WG do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for pyroxasulfone is adequate to define the majority of toxic effects that may result from exposure to pyroxasulfone. In short-term and chronic studies on laboratory animals, the primary targets were the liver in rodents, the heart in rats, the kidney in male mice, the urinary bladder in male rats, and the peripheral nerves and skeletal muscle in mice and dogs. There was evidence of tumourigenicity in the urinary bladders of male rats after longer-term dosing. A mode of action for the development of these tumours was supported and consequently, a threshold approach was applied for the cancer risk assessment. No treatment-related reproductive toxicity or birth defects were observed. Increased incidences of early and total resorptions per doe were observed in the rabbit developmental toxicity study. There was evidence of increased susceptibility of the young in the rat developmental neurotoxicity study, but not in rat reproduction or developmental toxicity studies. Pyroxasulfone is considered to be a neurotoxicant based on the occurrence of morphological changes in the brains of young rats, and nerve and muscle toxicity in rodents and dogs. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixer/loaders and applicators handling Pyroxasulfone 85 WG and workers re-entering treated fields are not expected to be exposed to levels of pyroxasulfone that will result in an unacceptable risk when Pyroxasulfone 85 WG is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residue in plants and animals is adequately understood. The residue definition is pyroxasulfone and the metabolite M3 for both enforcement and risk assessment purposes in plant commodities. The residue definition is pyroxasulfone for both enforcement and risk assessment purposes in livestock commodities. The proposed use of pyroxasulfone on field corn and imported sweet corn and popcorn does not constitute an unacceptable acute or chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits. The PMRA recommends that the following maximum residue limits be specified for:

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[9] DIR2006-02, *PMRA Formulants Policy*.

Commodity	Recommended MRL (ppm)
Field corn	0.015
Popcorn grain	0.015
Sweet corn kernels plus cob with husks removed	0.015
Eggs	0.01
Fat, meat and meat by-products of cattle, goats, hogs, horses, poultry, and sheep	0.01
Milk	0.001

7.2 Environmental Risk

Pyroxasulfone is moderately persistent to persistent in soil and aquatic systems under laboratory conditions. Pyroxasulfone and the major transformation product, KIH-485-M-1, residues have the potential to be mobile in soil and can be transported with water through the soil profile or with surface runoff to reach groundwater and surface water, respectively. Terrestrial field studies indicate that pyroxasuklfone and the major transformation product , KIH-485-M-1, would be less persistent under more realistic conditions of use. The transformation product, KIH-485-M-1 is persistent. Pyroxasulfone presents a negligible risk to terrestrial organisms at the proposed use rate. Pyroxasulfone is expected to pose a risk to freshwater vascular plants and green algae. In order to minimize the potential for exposure from spray drift, no-spray buffer zones between the treated area and downwind aquatic areas will be required. Precautionary labels statements regarding runoff will also be required. No environmental risk was identified from exposure to pyroxasulfone's major transformation product, KIH-485-M-1.

7.3 Value

The value data submitted in support of Pyroxasulfone 85 WG registration are adequate to determine efficacy in field corn. A single pre-plant surface, pre-emergence or early post-emergence application of Pyroxasulfone Herbicide at 145 to 290 g/ha provides control of green foxtail, yellow foxtail, giant foxtail, large crabgrass, barnyard grass, Italian ryegrass, redroot pigweed, and common waterhemp. Efficacy data also demonstrated that Pyroxasulfone 85 WG may be applied in combination with either glyphosate (present as isopropylamine, potassium, or diammonium salt) or atrazine for broader spectrum weed control or improved burndown.

The submitted phytotoxicity and yield data demonstrated an adequate margin of safety of field corn and soybeans to Pyroxasulfone 85 WG. Pyroxasulfone 85 WG provides an alternative mode of action to commonly used herbicides (i.e. Group 2, 3, and 5 Herbicide) for field corn and soybeans.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Pyroxasulfone Technical and Pyroxasulfone 85 WG, containing the technical grade active ingredient pyroxasulfone, to control weeds in field corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
amu	atomic mass unit
ARfD	acute reference dose
atm	atmosphere
ATPD	area treated per day
bw	body weight
CAF	composite assessment factor
cm	centimeter
d	day(s)
DNT	developmental neurotoxicity
DFR	dislodgeable foliar residue
DT_{50}	dissipation time 50%
DT_{90}	dissipation time 90%
dw	dry weight
EC_{25}	effect concentration 25%
EC_{50}	effect concentration 50%
EEC	estimated environmental concentration
EDE	estimated daily exposure
F_0	parental generation
FIR	food ingestion rate
g	gram
h	hour
ha	hectare(s)
HAFT	highest average field trial
HPLC-MS/MS	high performance liquid chromatography - tandem mass spectrometry
Kd	adsorption quotient
kg	kilogram
Koc	adsorption quotient normalized to organic carbon
Kow	octanol water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose 50%
LLNA	local lymph node assay
LOC	level of concern
LOEC	lowest-observed-effect-concentration
LOEL	lowest-observed-effect-level
log P_{ow}	octanol-water partition coefficient
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	meter
m^3	cubic metres

mg	milligram(s)
mm	millimetre(s)
MOE	margin of exposure
MRL	maximum residue limit
MTD	maximum tolerated dose
nm	nanometers
NOAEL	no observed adverse effect level
NOEC	no-observed-effect-concentration
NOEL	no-observed-effect-level
Pa	pascal
PCPA	*Pest Control Product Act*
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppm	parts per million
RAC	raw agricultural commodity
REI	restricted entry interval
RQ	risk quotient
$t_{1/2}$	half life
TC	transfer coefficient
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	toxic substances management policy
UF	uncertainty factor
µg	microgram
μL	micro litre
US	United States
USEPA	United States Environmental Protection Agency
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis in Soil and Water

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	ATM-0042-01	Pyroxasulfone	HPLC-MS/MS	0.002 mg/kg	1743522 and 1743523
		M-1			
		M-3			
Water	Not stated	Pyroxasulfone	HPLC-MS/MS	0.005 mg/L	1743524
		M-1			
		M-3			

Table 2 Residue Analysis in Plant and Animal Matrices

Analytical Methodology	
Parameters	**Plant Matrices**
Method ID	Not provided
Type	LC-MS/MS
Analytes	Pyroxasulfone, the metabolites M1, M3 and M25.
LOQ	0.005 ppm/analyte in corn matrices, except for M3 in corn meal and M1 in corn oil, which is 0.01 ppm.
References	PMRA#s 1817269, 1743514, 1743520 and 2041481
Parameters	**Animal Matrices**
Method ID	Not provided
Type	LC-MS/MS
Analytes	Pyroxasulfone, the metabolites M1 and M3.
LOQ	0.01 ppm/analyte in livestock commodities, except in milk, which is 0.001 ppm/analyte.
References	PMRA#s 1743704 and 1743518

Table 3 Toxicity Profile of End-use Product, Pyroxasulfone 85 WG Containing Pyroxasulfone

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Pyroxasulfone 85 WG	
Acute oral toxicity Wistar rats PMRA #1743534	Female LD_{50} > 2000 mg/kg bw Low toxicity

Study Type/Animal/PMRA #	Study Results
Acute dermal toxicity Wistar rats PMRA #1743940	LD_{50} > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Wistar rats PMRA #1743942	LC_{50} > 5.8 mg/L Low toxicity
Dermal irritation NZW rabbits PMRA #1743950	MAS = 0.44/110 MIS = 1.0/110 Minimally irritating
Eye irritation NZW rabbits PMRA #1743952	MAS = 1.8/110 MIS = 4.7/110 Minimally irritating
Dermal sensitization (Buehler test) Dunkin Hartley guinea pigs PMRA #1743956	Potential skin sensitizer

Table 4 Toxicity Profile of Technical Pyroxasulfone

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Wistar rats PMRA #1743534	Female LD_{50} > 2000 mg/kg bw Low toxicity
Acute dermal toxicity Wistar rats PMRA #1743535	LD_{50} > 2000 mg/kg bw Low toxicity

Study Type/Animal/PMRA #	Study Results
Acute inhalation toxicity Wistar rats PMRA #1743536	$LC_{50} > 6.56$ mg/L Low toxicity
Dermal irritation NZW rabbits PMRA #1743537	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbits PMRA #1743538	MAS = 0.22/110 MIS = 6.0/110 Minimally irritating
Dermal sensitization (LLNA) CBA/JHsd mice PMRA #1743539	No clinical signs, body weight effects or increases in cell proliferation index. The positive control validated the study methods used. Non-sensitizer
28-day dermal Sprague-Dawley rats PMRA #1743573	Systemic Toxicity and Dermal Irritation: NOAEL: 100 LOAEL: 1000, based on increased cardiac myofiber degeneration/inflammation; cutaneous myofiber degeneration with inflammation in treated skin (M); mucosal inflammation in the cecum; perivascular inflammation in the lung; singular incidence of myofiber degeneration in the sternal muscle (M)
28-day inhalation toxicity Sprague-Dawley rats PMRA #1743572	NOAEL: 4.02 mg/L (equivalent to approximately 40.78/50.49 mg/kg bw/day M/F) LOAEL: not established
28-day dietary toxicity Wistar Rats PMRA #1743540	NOAEL: 64.3/62.2 LOAEL: 649.7/673.9, based on increased clinical chemistry parameters; increased liver weights; enlarged mottled and pale livers; hepatocyte vacuolation; myocardial vacuolation; myocardial degeneration/necrosis
90-day dietary toxicity CD-1 mice PMRA#1743553-1743554	NOAEL: 394.0/51.2 mg/kg bw/day M/F LOAEL: Not established/531.3 mg/kg bw/day M/F, based on increased chronic progressive nephropathy in females.
90-day dietary toxicity B6C3FR1 mice PMRA#1743552	NOAEL: 206/202 mg/kg bw/day M/F LOAEL: 1421/1228 mg/kg bw/day M/F, based on increased clinical signs, decreased body weight/gains and food consumption; increased clinical chemistry parameters; increased liver weights; enlarged and mottled livers; hepatocellular hyperptrophy/vacuolation; myocardial degeneration/fibrosis at an excessive dose level.

Study Type/Animal/PMRA #	Study Results
90-day dietary toxicity Wistar rats PMRA#1743542, 1743543, 1743544	NOAEL: 44/49 LOAEL: 221.4/255.9, based on decreased body weight/gains, food efficiency; reduced motor/locomotor activity; myocardial necrosis/degeneration; myopathy of skeletal muscle
90-day dietary toxicity Sprague-Dawley rats PMRA#1743547, 1743549, 1743551	NOAEL: 16.4/20.6 LOAEL: 171.2/205.4, based on increased clinical chemistry parameters; cardiac myofiber degeneration/inflammation; diffuse mucosal hyperplasia of bladder (M); degeneration of myofibers of sternal muscle (F); quadriceps degeneration/inflammation (F)
90-day capsule toxicity Beagle dogs PMRA#1743555 Acceptable when reviewed in conjunction with PMRA #1743555; in isolation, supplemental	NOAEL: 2/10 LOAEL: 10/not established, based on degeneration of muscle fibre in the diaphragm (multifocal) & diffuse hyperplasia of satellite cells of the muscle & nerve fibre degeneration of sciatic nerve (focal) in one male.
1-year capsule toxicity Beagle dogs PMRA #1743557, 1743559, 1743560, 1743570, 1743571	NOAEL: not established LOAEL: 15, based on decreased body weight gain and thin appearance (males); abnormal limb function; increased creatinine kinase; sciatic nerve degeneration; subacute inflammation of skeletal muscle of diaphragm, superficial digital flexor or biceps femoris; myofiber degeneration of the biceps femoris or superficial digital flexor (male)
1-year dietary toxicity Sprague-Dawley rats PMRA #1743557-1743580	NOAEL: 2.22/3.12 LOAEL: 46.20/60.80, based on decreased body weight/gains and food efficiency (male); increased incidence & severity cardiomyopathy (female); mucosal hyperplasia and inflammation of urinary bladder (male)
Carcinogenicity (18-month dietary) CD-1 mice PMRA #1743599, 1743601, 1743605, 1743606, 1743609, 1743611, 1743613, 1743616, 1743617, 2041485	NOAEL: 18.56/22.44 LOAEL: 131.34/76.49, based on premature deaths in 5 females due to clinical signs secondary to sciatic nerve degeneration; abnormal limb gait and decreased muscle tone; decreased body weight/gains and food efficiency; nerve and spinal cord degeneration; tubular nephrosis, intratubular precipitate, tubular hyperplasia; increased severity of chronic progressive nephropathy **No evidence of carcinogenicity.**
Chronic/ Carcinogenicity (2-year dietary) Sprague-Dawley rats PMRA #1743584, 1743585, 1743589, 1743590, 1743591, 1743593, 1743594, 1743595, 1743598, 2041484	NOAEL: 2.05/2.69 LOAEL: 42.55/54.28, based on decreased body weight/gains and food consumption (females); red stained urine on cage boards (males); cardiomyopathy; increased incidence and severity of urinary bladder mucosal hyperplasia & mucosal inflammation (males); sciatic nerve degeneration (females). **Evidence of tumourigenicity** (benign urinary bladder transitional cell papillomas) in males at the mid and high dose levels. A threshold-based mechanism for tumour formation was accepted by the PMRA.

Study Type/Animal/PMRA #	Study Results
One-generation reproduction Sprague-Dawley rats PMRA #1743618-1743619	NOAELs were not established since this study was considered supplemental. Parental effects included decreased body weight and body weight gain at the mid and high dose levels. There was no evidence of reproductive toxicity. Offspring body weights were decreased during lactation and vaginal opening was delayed at the mid and high dose levels. Delayed preputial separation was noted at the high dose.
Two-generation reproduction Sprague-Dawley rats PMRA #1743620, 1743621, 1743622, 1743623, 1743625, 1743626, 1743627	Parental toxicity: NOAEL: 5.75/6.94 LOAEL: 114.24/135.41, based on decreased body weight/gains, food consumption; cardiomyopathy (females); sciatic nerve degeneration (F0 females); mucosal hyperplasia in the urinary bladder; inflammation of the urinary bladder (males). Offspring toxicity: NOAEL: 5.75/6.94 LOAEL: 114.24/135.41, based on decreased body weights at birth and throughout lactation (associated with increased litter size). Reproductive toxicity: NOAEL: 114.24/135.41 LOAEL: not established
Developmental toxicity (range-finding) Sprague-Dawley rats PMRA #1743628	NOAELs were not established since this study was considered supplemental. There were no treatment-related maternal or developmental effects.
Developmental toxicity Sprague-Dawley rats PMRA #1743629	Maternal: NOAEL: 1000 LOAEL: not established Developmental: NOAEL: 1000 LOAEL: not established
Developmental toxicity (range-finding) New Zealand White rabbits PMRA #1743630	NOAELs were not established since this study was considered supplemental. There were no treatment-related maternal or developmental effects.
Developmental toxicity New Zealand White rabbits PMRA #1743630	Maternal: NOAEL: 500 LOAEL: 1000, based on increased early and total resorptions per dam Developmental: NOAEL: 500 LOAEL: 1000, based on decreased fetal weights and increased early and total resorptions per dam

Study Type/Animal/PMRA #	Study Results
Developmental toxicity New Zealand White rabbits PMRA #1743631	Maternal: NOAEL: 500 LOAEL: 1000, based on increased early and total resorptions per dam Developmental: NOAEL: 500 LOAEL: 1000, based on decreased fetal weights and increased early and total resorptions per dam
Acute neurotoxicity Sprague-Dawley rats PMRA #1743633	Neurotoxicity: NOAEL: 2000 LOAEL: not established No evidence of neurotoxicity.
Subchronic neurotoxicity Sprague-Dawley rats PMRA #1743634	Systemic Toxicity & Neurotoxicity: NOAEL: 15.85/19.60 LOAEL: 161.48/199.59, based on decreased body weight/gains; mild myofiber degeneration in gastrocnemius muscle (1 female)
Developmental neurotoxicity (range-finding) Sprague-Dawley rats PMRA #1743636	NOAELs were not established since this study was considered supplemental. Only minor treatment-related offspring effects were observed at a limit dose (increased body weight gains secondary to smaller litter size; increased liver weights)
Developmental neurotoxicity Sprague-Dawley rats PMRA #1743637, 1743639, 1817257, 1817260, 1817262, 1817263, 1817264, 1817265, 1817266	Systemic Toxicity: NOAEL: 900 LOAEL: not established Neurotoxicity: NOAEL: 100 LOAEL: 300, based on decreased absolute and relative brain weights, decreased hippocampus thickness, corpus callosum thickness and decreased thickness of pyramis folia of cerebellum in PND 21 females.
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743574	Negative
Gene mutations in mammalian cells in vitro Mouse lymphoma L5178Y cells PMRA #1817249	Negative
In vitro mammalian chromosomal aberration Chinese hamster ovary cells PMRA #1743575	Negative

Study Type/Animal/PMRA #	Study Results
In vivo mammalian cytogenetics Crl:CD-1(ICR) mice PMRA #1743576	Negative
28-day immunotoxicity dietary CD-1 mice PMRA #1743533	Systemic Toxicity: NOAEL: 61/77 LOAEL: 633/791, based on decreased body weight/gains, food efficiency. Immunotoxicity: NOAEL: 633/791 LOAEL: not established No evidence of immunosuppression.
28-day immunotoxicity dietary Sprague-Dawley rats PMRA #1743532	Systemic Toxicity: NOAEL: 18/19 LOAEL: 529/570, based on decreased body weight/gains, food consumption and food efficiency. Immunotoxicity: NOAEL: 529/570 LOAEL: not established No evidence of immunosuppression.
Lacteal secretion (gavage)-supplemental Sprague-Dawley rats PMRA #1743529	NOAELs were not established since this study was considered supplemental. The objective of this study was to investigate the levels of radioactivity in milk and plasma of lactating rats on lactation day 10. Results suggested that a single high dose of radioactivity is secreted into the milk of maternal rats.
Transfer of radioactivity into stomach contents of rat offspring following repeated gavage dosing in dams-supplemental Sprague-Dawley rats PMRA #1743527	NOAELs were not established since this study was considered supplemental. The objective of this study was to investigate the secretion of radioactivity into milk of nursing mothers by analysis of pup stomach contents. The lower concentrations of radioactivity in pup stomach contents compared to maternal plasma suggested that there was limited active transport of radioactivity into the milk.
28-day dietary – investigation of creatinine phosphokinase (CPK) and heart toxicity-supplemental Wistar rats PMRA #1817248	NOAELs were not established since this study was considered supplemental. The objective of this study was to investigate the enzyme markers and the onset of potential degeneration and necrosis in the heart following treatment with pyroxasulfone. Results indicated that CPK enzymes were not predictive markers for myocardial toxicity and that myocardial degeneration/necrosis was observed as early as day 8 in females.

Study Type/Animal/PMRA #	Study Results
Effects on motor systems after 14-day dietary exposure to pyroxasulfone (glutathione depletion animal model) CD-1 mice PMRA#1879690, 1879692	To clarify the relationship between pyroxasulfone-induced motor system effects and intracellular glutathione (GSH) concentrations, a GSH depletion animal model was employed in mice. The results suggested that pyroxasulfone augments the effects of BSO, a known depleter of glutathione. The results of this study were confounded by the absence of a control group treated with pyroxasulfone alone. In addition, there were no attempts to measure glutathione levels in muscle tissues biochemically.
14-day Cell Proliferation Activity and Oxidative Stress in Mouse Kidney CD-1 mice PMRA#1879694	To investigate the modes of action of pyroxasulfone on mouse kidney, particularly cell proliferation activity and oxidative stress in renal epithelial cells. The results demonstrated that pyroxasulfone does not cause cell proliferation activity or oxidative stress in the mouse kidney under the study conditions tested.
14-day Cell Proliferation Activity and Oxidative Stress in Rat Urinary Bladder Sprague-Dawley rats PMRA #1879695	To investigate the modes of action of pyroxasulfone on the rat urinary bladder, particularly cell proliferation activity and oxidative stress. The results demonstrated that pyroxasulfone treatment causes increased cell proliferation associated with cell hyperplasia in the urinary bladder epithelium. It is not likely that oxidative stress is involved with urothelial hyperplasia under the study conditions tested.
Scanning Electron Microscopic (SEM) Examination of Rat Urinary Bladder after 14-days of treatment Sprague-Dawley rats PMRA #1879691	To elucidate the mode of action of the bladder hyperplastic effect in pyroxasulfone-treated male rats. A hyperplastic effect in the bladder epithelium was detected by SEM. There was no evidence of microcrystals. The cause of the observed urothelial hyperplasia observed in the male rat is not known.
In vivo Comet assay CD-1 mice PMRA#1879696	To assess the DNA reactivity of pyroxasulfone in the kidney and liver of male mice using an in vivo comet test system and to clarify the non-genotoxicity in the kidney where low incidence of tumour formation occurred in the 18-month carcinogenicity feeding study in mice. Pyroxasulfone treatment caused an increase in the tail intensity (DNA strand breaks) in the kidneys of male mice. The positive control validated the test methods used.
In vivo Comet assay Sprague-Dawley rats PMRA #1879697	To assess the DNA reactivity of pyroxasulfone in the urinary bladder and liver of male rats using an in vivo comet test system and to clarify the non-genotoxicity in the urinary bladder where low incidence of tumour formation occurred in the two year carcinogenicity feeding study in rats. Pyroxasulfone treatment caused an increase in the tail intensity (DNA strand breaks) in the bladder and liver cells of male rats. The positive control validated the test methods used.
Pyroxasulfone Mode of Action: Weight-of-Evidence for Carcinogenicity PMRA #2004550	

Study Type/Animal/PMRA #	Study Results
Expert pathologist opinion on mouse renal tumours: Amended Report: Expert Report on Kidney Histopathology in Toxicology/Carcinogenicity Studies with KIH-485 TGAI (Pyroxasulfone) Administered in the Feed to CD-1 Mice PMRA #2041482	Pyroxasulfone treatment was associated with an ascending form of nephropathy presumably arising secondarily from an effect in the lower urinary tract, possibly formation of urinary solids. There was no evidence of tubule cytotoxicity or a cell proliferation response. In the expert pathologist's opinion, based on the absence of any cytotoxicity or cell regeneration, and the random distribution of tumours between dose groups, the renal adenomas were of spontaneous origin and unrelated to administration of the test compound. It was concluded that pyroxasulfone is not carcinogenic for mouse kidney.
Pathology Working Group to Examine Histopathologic Changes Reported in the Kidneys of Mice in Toxicology and Carcinogenicity Studies with Pyroxasulfone PMRA #2004557	The results of this Pathology Working Group review of histopathologic changes reported in the kidneys of male mice in toxicology and carcinogenicity studies with pyroxasulfone supported the conclusion that pyroxasulfone is not carcinogenic for the mouse kidney. There was no evidence of increased incidences of pre-neoplastic changes, including no evidence of cytotoxicity or regenerative hyperplasia. An increase in the incidence and severity of retrograde nephropathy was present in test substance-treated male mice as compared to control male mice. This finding may have been related to the formation of a renal precipitate that resulted in the obstructions of lower urinary passages. Retrograde nephropathy was a distinct entity, unassociated with tubular epithelial toxicity or regeneration, that was consistently distinguished from chronic progressive nephropathy that frequently is observed in the kidneys of aged mice. The incidence and severity of chronic progressive nephropathy was not altered by treatment with pyroxasulfone in treated male mice as compared to controls.
Expert pathologist opinion on rat bladder tumours: The Effects of Dietary Administration of Pyroxasulfone on the Urinary Bladder of Male Rats PMRA #2041483	The present experiment demonstrated that the increased proliferation in the urothelium of the rat bladder following oral administration of pyroxasulfone is due to cytotoxicity, necrosis, and regeneration. The presence of crystals in the present experiment and the observation of calculi in the two-year bioassay strongly suggest that the cytotoxicity is due to the formation of urinary solids (composition not clear at this time). Evidence suggests that the solids, crystals and calculi, are only intermittently and transiently present. This is consistent with the nature of (i.e. composition and size) of the solids since calculi will be retained only if they are larger than the diameter of the urethra as it exits the bladder. Calculi can either enlarge or become smaller depending on the volume of urine and the concentration of the solutes over time, as the crystallization process is dynamic, not static.

Study Type/Animal/PMRA #	Study Results
Review of Selected Slides from the Bladders of Male Rats from the Two-Year Carcinogenicity Bioassay on Pyroxasulfone PMRA #2004558	The slides of urinary bladders from the male rats that had been diagnosed either with carcinoma, papilloma, or extensive proliferative lesions of the bladders and sections of mouse kidneys from selected animals with the most extensive changes were re-examined by an expert pathologist. The original study pathologist diagnosed papilloma in 8 animals and 1 carcinoma. The expert pathologist concurred with the diagnosis of the study pathologist in all instances except for the 1 case in which a lesion was classified as carcinoma. Based on the histological characteristics of this lesion, it was the opinion of the expert pathologist that the epithelium is clearly benign in appearance throughout the bladder in question.
Metabolism Sprague-Dawley rats PMRA #1743582, 1743583, 1743525	**Absorption** Pyroxasulfone was rapidly and well absorbed, as determined in a single oral low dose bile-cannulation study. At the high-dose, absorption was greater than 26% administered dose (AD) indicating saturation of routes of absorption. The pharmacokinetics of pyroxsulfone were not linear with respect to dose. **Distribution** Pyroxasulfone was rapidly and widely distributed in the body. The highest radioactive residues were observed in the gastrointestinal tract, kidney, blood (red blood cells), liver, heart, lung, spleen and skin. Following repeat dosing, concentrations were detected in the uterus, ovaries, pancreas, bone marrow and thymus. Total radioactivity remaining in the carcass was less than 4% AD. There was no evidence of bioaccumulation. **Excretion** The majority of fecal and urinary excretion occurred within the first 24 hours. The primary route of excretion was via the urine, except for the single oral high dose which showed predominantly fecal excretion. There were no apparent differences in excretion after repeat dosing in females, other than slightly higher urinary excretion. Biliary excretion accounted for approx. 13-37% AD. Less than 5% AD was isolated in the carcass and tissues, and less than 9% AD was found in the cage wash and debris. There were no significant levels of pyroxasulfone in expired air (less than 2% AD). **Metabolism** Pyroxasulfone was extensively metabolized. The primary route involved the cleavage of the sulfonyl group and subsequent sequential oxidations of this group on the pyrazole moiety or glutathione conjugation and subsequent hydrolysis of the isoxazoline moiety. The second route involved sequential oxidations of the parent compound. Most of the urinary metabolites were produced by the cleavage between the pyrazole and isoxazoline ring. The major component of the feces was unabsorbed pyroxasulfone. In the bile, the major metabolites were 2 conjugated compounds co-chromatographing with a sulphate conjugate of hydroxy-pyroxasulfone, M-13 and M-26.
Metabolism-supplemental CD-1 mice (females) PMRA #1743531	**Absorption** Absorption was not estimated for the mouse. **Distribution** Pyroxasulfone was rapidly and widely distributed in the body (within 2 hours post-dosing). The highest radioactive residues observed by autoradiography were in the Harderian gland, lachrymal glands, lungs, ovaries, pituitary, salivary glands, skin, spleen, tongue and uterus and especially in organs of excretory function or their contents. The high concentrations in the liver and gallbladder are consistent with efficient first-pass elimination by the liver, followed by biliary excretion. More moderate radioactivity levels were observed in fat, adrenals, bone marrow, mammary tissue, myocardium, pancreas, skeletal muscle and thymus. Low levels were detected on bone surfaces, brain, spinal cord and the lens of the eye. By 24 hours, the radioactivity concentration in the majority of tissues was close to or indistinguishable from

Study Type/Animal/PMRA #	Study Results
	background. Low levels of radioactivity were still present in a number of organs by 48 hours. Distribution in the liver and heart was highest at 2 hours and declined thereafter. **Excretion** The majority of fecal and urinary excretion occurred within the first 24 hours. The primary route of excretion was via the urine. **Metabolism** Pyroxasulfone was extensively metabolized. The major urinary metabolites were M-3, M-1 and M-13. One metabolite, a glucuronide or sulfate conjugate was present at 4% AD and was not detectable after enzyme treatment. The major component of the feces was unabsorbed pyroxasulfone. In the bile, the major metabolites were 2 conjugated compounds co-chromatographing with a sulphate conjugate of hydroxy-pyroxasulfone, M-13 glucuronide and M-26.
Metabolism-supplemental Beagle dogs (females) PMRA #1743528	**Absorption** Absorption was not estimated for the dog. **Distribution** Pyroxasulfone was rapidly and widely distributed in the body (within 8 hours post-dosing in the blood and plasma). The terminal half-lives in the blood and plasma were 90 hours and 40 hours, respectively. The radioactivity levels in the carcass, liver, kidney and heart totalled 1.3% AD at 120 hours. **Excretion** The majority of fecal and urinary excretion occurred within the first 24 hours. The primary route of excretion was via the urine. **Metabolism** Pyroxasulfone undergoes metabolism at three sites, one of the methyl group of the isoxazole ring, the sulfur atom and the N-methyl group in the pyrazole ring. Metabolite F was produced from the oxidation of methyl group on the isoxazole ring to the corresponding carboxylic acid and represented the major urinary metabolite in the dog. Other urinary metabolites produced after β-D-glucuronidase treatment included M-3, M-8, M-7 and glucuronide conjugates. In the feces, only unchanged parent compound was detected.
METABOLITE STUDIES – M-1	
Acute oral Sprague-Dawley rats PMRA #1743640	Female LD_{50} >2000 mg/kg bw Low Toxicity
14-day gavage – supplemental Wistar rats (females) PMRA #1743651	NOAELs were not established since this study was considered supplemental. The only effects observed were decreased body weights and decreased kidney and spleen weights at 1000 mg/kg bw/day.
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743653	Negative

Study Type/Animal/PMRA #	Study Results
METABOLITE STUDIES – M-3	
Acute oral Sprague-Dawley rats PMRA #1743646	Female LD_{50} > 2000 mg/kg bw Low Toxicity
14-day gavage – supplemental Wistar rats (females) PMRA #1743652	NOAELs were not established since this study was considered supplemental. There were no treatment-related effects up to 1000 mg kg bw/day.
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743654	Negative
METABOLITE STUDIES – M-25	
Acute oral Wistar rats PMRA #1743647	Female LD_{50} > 2000 mg/kg bw Low Toxicity
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743655	Negative
METABOLITE STUDIES – M-28	
Acute oral Sprague-Dawley rats PMRA #1743659	Female LD_{50} > 2000 mg/kg bw Low Toxicity
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743660	Negative
IMPURITY STUDIES – I-3	
Acute oral Sprague-Dawley rats PMRA #1743648	Female LD_{50} > 2000 mg/kg bw Low Toxicity

Study Type/Animal/PMRA #	Study Results
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743656	Negative
IMPURITY STUDIES – I-4	
Acute oral Sprague-Dawley rats PMRA #1743649	Female LD_{50} >2000 mg/kg bw Low Toxicity
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743657	Negative
IMPURITY STUDIES – I-5	
Acute oral Sprague-Dawley rats PMRA #1743650	Female LD_{50} >2000 mg/kg bw Low Toxicity
Reverse gene mutation assay *Salmonella typhimurium, E.Coli* PMRA #1743658	Negative

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Pyroxasulfone

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Developmental neurotoxicity study	NOAEL = 100 Decreased brain weights and decreased brain morphometrics (hippocampus, corpus callosum, cerebellum) in PND 21 females	1000
	ARfD = 0.10 mg/kg bw		
Repeated dietary	12-month dog toxicity study	NOAEL = 2 Impaired hindlimb function and other neurotoxic effects; clinical pathology; axonal/myelin degeneration of the sciatic nerve and spinal cord	100
	ADI = 0.02 mg/kg bw/day		
Short-term dermal[2]	Developmental neurotoxicity study	NOAEL = 100 Decreased brain weights and decreased brain morphometrics (hippocampus, corpus callosum, cerebellum) in PND 21 females	1000
Short-term inhalation[3]			

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Intermediate –term dermal[2]	12-month dog toxicity study	NOAEL = 2 Impaired hindlimb function and other neurotoxic effects; clinical pathology; axonal/myelin degeneration of the sciatic nerve and spinal cord	100
Intermediate-term inhalation[3]			
Cancer	There was adequate evidence to support a threshold-based mechanism to the urinary bladder transitional cell papillomas in male rats. The dietary reference dose (i.e. the ADI) and the selected MOEs for occupational and bystander exposure provide a sufficient margin to this tumour.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 100% was used in a route-to-route extrapolation

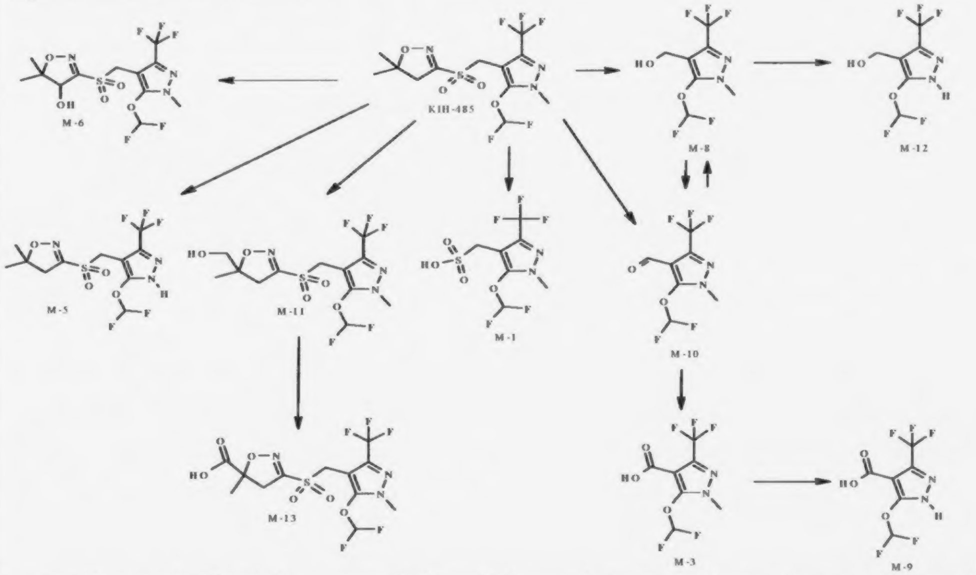
[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 Integrated Food Residue Chemistry Summaries

NATURE OF THE RESIDUE IN ANIMALS - HEN			PMRA#s 1743669, 1743670, 2104547, and 2041490	
Radiolabel Position	[Pyrazole-14C] and [Isoxazoline-14C] Pyroxasulfone			
Laying hens (5 animals per treatment group) were dosed orally once daily with either [pyrazole-14C] pyroxasulfone or [isoxazoline-14C] pyroxasulfone at a rate equivalent to 10 ppm in the feed for 10 and 3 consecutive days, respectively. Samples of excreta were collected daily. Samples of eggs were collected twice daily. The treated hens were sacrificed approximately 23 hours after the final dosage and samples of liver, skin, muscle and fat were collected. Each tissue was processed as a single pooled sample per radiolabel.				
Matrices	[pyrazole-14C]		[isoxazoline-14C]	
	TRRs (ppm)	% AD	TRRs (ppm)	% AD
Excreta	-	80.1	-	99.5
Egg Yolk	0.120	0.060	0.098	0.064
Egg White	0.027	0.058	0.106	0.228
Blood	0.11	-	0.036	-
Plasma	0.058	-	0.192	-
Muscle	0.11	0.103	0.041	0.222
Fat	0.022	0.002	0.009	0.004
Liver	0.50	0.109	0.115	0.131
Skin	0.049	0.004	0.033	0.015
Cage Wash	-	1.33	-	3.042
Total % AD	87.7		103.2	
Metabolite Identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel Position	[Pyrazole-14C]	[Isoxazoline-14C]	[Pyrazole-14C]	[Isoxazoline-14C]
Egg Yolk	-	M13	Pyroxasulfone, M1, M5, M6, M8, M9, M10 and M12	M5, M11 and M13
Egg White	M12	-	M5 and M6	M11 and M13

Liver	-	-	M1, M3, M8 and M12.	pyroxasulfone
Muscle	-	N/A	M1, M3 and M10	N/A
Fat	-	N/A	Pyroxasulfone and M12	N/A
Skin	-	-	Pyroxasulfone, M3, M5, M11, M12 and M13	M13

Proposed metabolic scheme in hens:



Pyroxasulfone metabolism in hens proceeds through cleavage between the rings to form metabolites M1, M8, and M10. Oxidation of M10 would yield metabolite M3, and metabolites M12 and M9 could be formed via demethylation of M8 and M3, respectively. Hydroxylation of pyroxasulfone would yield metabolites M6 and M11, and further oxidation of M11 would yield M13. Metabolite M5 could be formed via demethylation of pyroxasulfone.

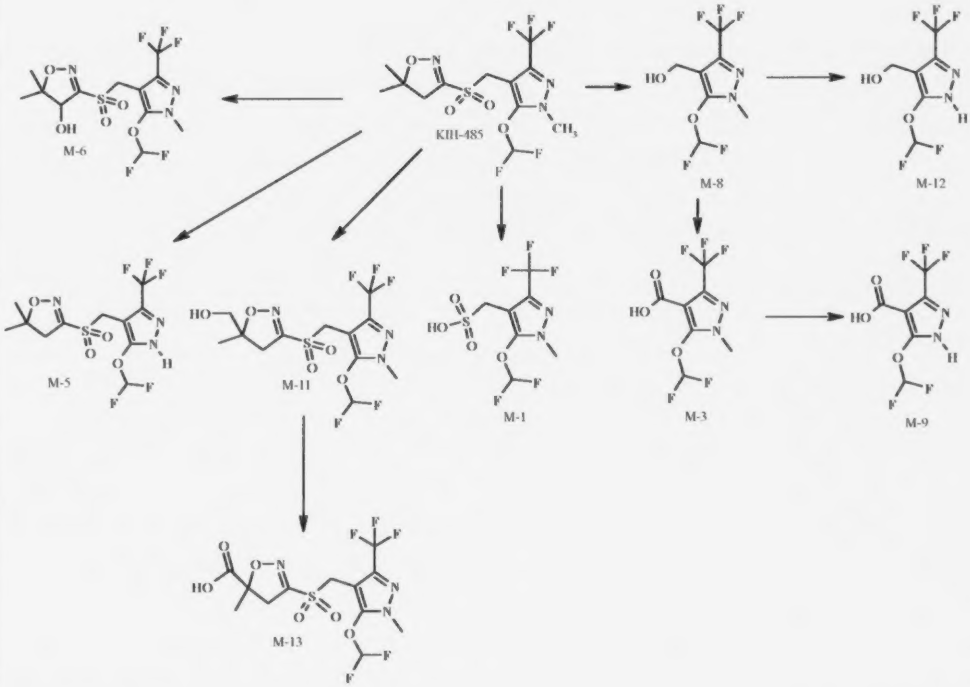
NATURE OF THE RESIDUE IN ANIMALS - GOAT	PMRA#s 1743671, 1743672, 1743673, 2104553, and 2041492
Radiolabel Position	[Pyrazole-14C] and [Isoxazoline-14C] Pyroxasulfone

Lactating goats (1 animal per treatment group) were dosed orally once daily with either [pyrazole-14C] pyroxasulfone or [isoxazoline-14C] pyroxasulfone at a rate equivalent to 10 ppm in the feed for 5 and 3 consecutive days, respectively. Samples of excreta were collected daily. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver and kidney) were collected at sacrifice. Milk and tissues were processed as pooled samples for each radiolabel.

Matrices	[pyrazole-14C]		[isoxazoline-14C]	
	TRRs (ppm)	% AD	TRRs (ppm)	% AD
Urine	-	83.84	-	60.66
Feces	-	4.361	-	11.21
Cage Wash	-	3.389	-	8.320
Milk	0.0265 (Day 5 pm)	0.074	0.0912 (Day 3 pm)	0.418
Plasma	0.004643	-	0.3617	-
Blood	0.005192	-	0.2909	-
Renal Fat	<LOQ	<LOQ	0.039914	0.013
Kidney	0.01713	0.003	0.2904	0.071

Liver	0.2181	0.226	0.8989	1.219
Muscle	0.003408	0.006	0.06583	0.110
Omental Fat	0.001506	0.001	0.03863	0.029
Total % of AD	91.9		82.05	
Metabolite Identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel Position	[pyrazole-14C]	[isoxazoline-14C]	[pyrazole-14C]	[isoxazoline-14C]
Muscle	N/A	-	N/A	M22
Kidney	-	-	M1, M5 or M6, M8, and M12	M6, M15, M22 and pyroxasulfone
Liver	-	-	M1, M3, M5 or M6, M8, M9, M11, and M12	M5, M13, M16 and M22
Milk	M13	-	M1, M3, M8, M9, M11, M12 and M13	M13, M16 and M22

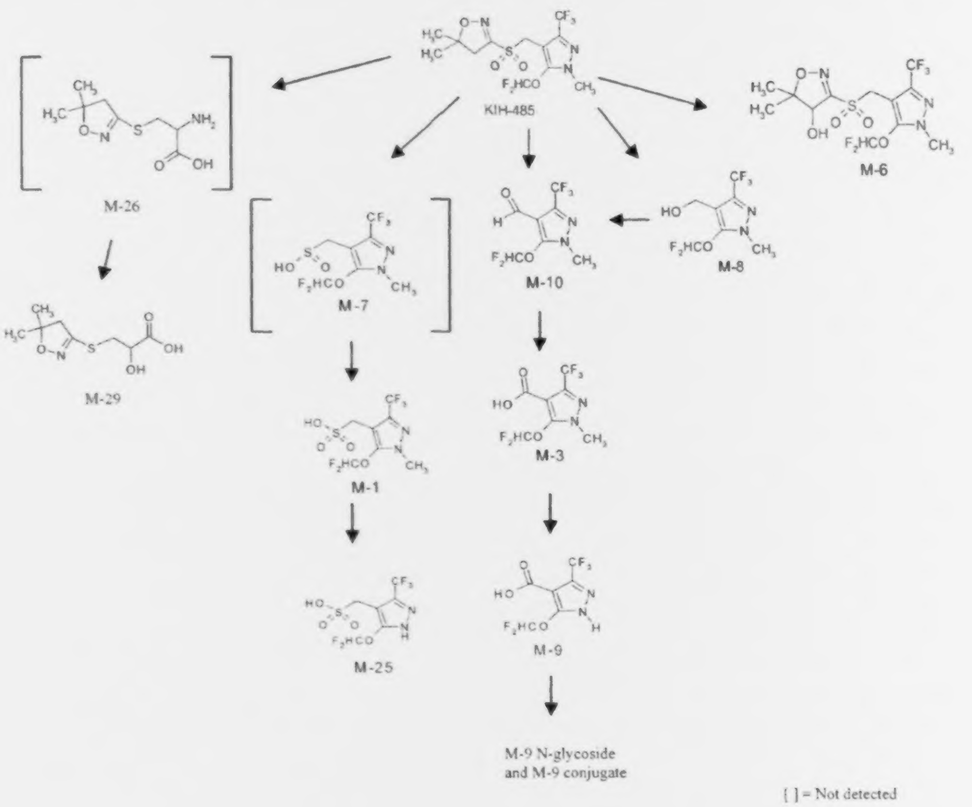
Proposed metabolic scheme in goats:



Pyroxasulfone metabolism in goats proceeds through cleavage between the rings to form metabolites M1 and M8. Oxidation of M8 would yield metabolite M3, and metabolites M12 and M9 could be formed via demethylation of M8 and M3, respectively. Hydroxylation of pyroxasulfone would yield metabolites M6 and M11, and further oxidation of M11 would yield M13. Metabolite M5 could be formed via demethylation of pyroxasulfone.

NATURE OF THE RESIDUE IN PLANTS - Corn	PMRA#s 1743662 and 2011486
Radiolabel Position	[Pyrazole-14C] and [Isoxazoline-14C] Pyroxasulfone
Test site	Outdoors
Treatment	Broadcast spray

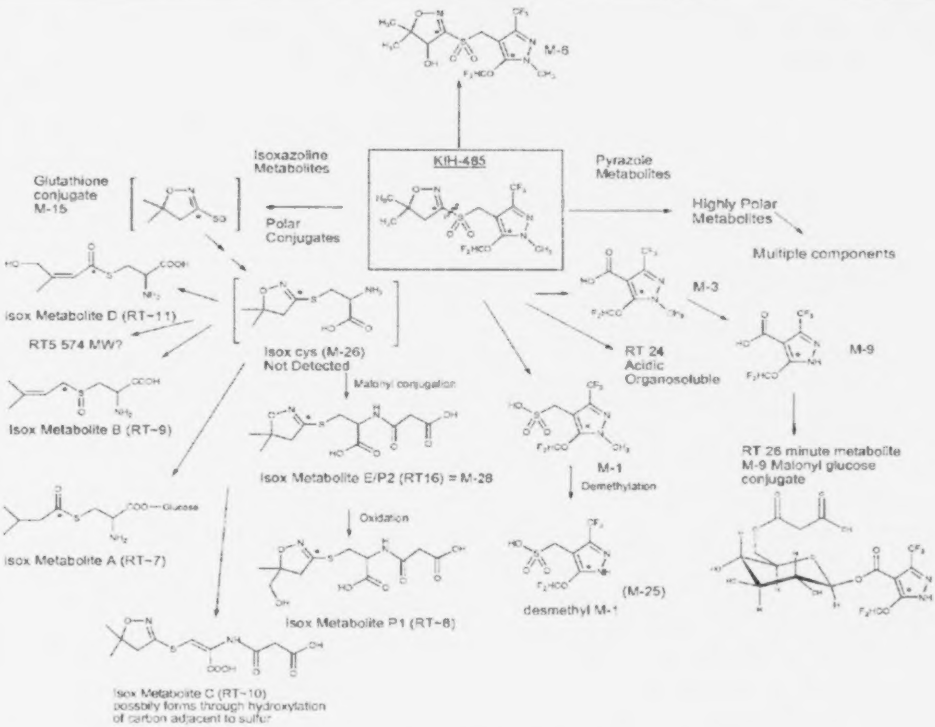
Rate	1500 g a.i./ha (~5x GAP)			
Timing	Pre-emergence or early post-emergence (growth stage V4)			
Preharvest interval	Corn foliage: 28-149 days. Corn grain: 105-149 days.			
End-use product	Formulated as a water dispersible granules 85% (w/v)			
TRRs in Corn Raw Agriculture Commodities				
Matrix	Pre-emergence		Post-emergence	
	[pyrazole-14C] (ppm)	[isoxazoline-14C] (ppm)	[pyrazole-14C] (ppm)	[isoxazoline-14C] (ppm)
Mature Foliage	2.474	3.250	3.315	2.894
Mature Root	2.052	3.438	0.835	0.980
Mature Kernel	0.132	0.101	0.024	0.048
Metabolite Identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel Position	[pyrazole-14C]	[isoxazoline-14C]	[pyrazole-14C]	[isoxazoline-14C]
Mature Foliage	Pyroxasulfone, M1 and M25	Pyroxasulfone and M29	M3, M6, M8, M9 and M10	-
Mature Root	M1, and M25	-	Pyroxasulfone, M3, M6, M8, M9, M10	Pyroxasulfone and M29
Mature Kernel	-	-	M1, M3 and M25	M29
Proposed metabolic scheme in plants:				



Pyroxasulfone is metabolized in corn via cleavage of the methyl sulfone bridge of the parent, forming an intermediate metabolite (M7, which was not found in corn matrices) which undergoes oxidation to form the sulfonic acid metabolite M1. Metabolite M25 is formed following demethylation of M1. For the other pyrazole-ring metabolites, the carboxylic acid metabolite M3 likely forms from metabolites M8 and M10, with subsequent demethylation to form M9, which may be further conjugated. In the case of the isoxazoline-ring metabolites, an intermediate cysteine conjugate (M26, which was not found) may form from pyroxasulfone; subsequent deamination of M26 would result in the formation of the conjugate M29.

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Radish, Soybean and Wheat				**PMRA#s 1743708 and 2041500**	
Radiolabel Position		[pyrazole-14C]		[isoxazoline-14C]	
Test site		Outdoor, California, USA			
Formulation used for trial		85% WG			
Application rate and timing		300 g a.i./ha (~1x GAP)			
Metabolites Identified		Major Metabolites (> 10% TRRs)		Minor Metabolites (< 10% TRRs)	
Matrix	PBI (days)	[pyrazole-14C]	[isoxazoline-14C]	[pyrazole-14C]	[isoxazoline-14C]

Wheat grain	30	M3	M28, Metabolites P1, and B	M1, M9, M25 and M9 malonyl glucoside	Metabolite D
	120	M3	M28, Metabolite A	M1	Metabolite B
	365	M3	M28, and Metabolite B	M1 and M9	Metabolites A and C
Soybean seed	30	-	M28, and Metabolite P1	M1, M9, M25 and M9 malonyl glucoside	M6, and Metabolites A, C, and D
	120	-	M28, and Metabolite P1	M1, M3 and M9	-
	365	-	-	M1, M3, M9 and M25	-
Radish root	30	M1 and M9 malonyl glucoside	Metabolite P1	Pyroxasulfone, M3, M6, M9, and M25	Pyroxasulfoen, M28, and Metabolites A, C and D
	120	-	Metabolites A and B	Pyroxasulfone, M1 and M25	Pyroxasulfoen, M28, and Metabolite C and D
	365	-	Metabolites A and D	M1 and M25	M28, and Metabolites C and P1
Proposed metabolic scheme in rotational crops (wheat, radish and soybean):					


M-6
KIH-485
Isoxazoline Metabolites
Pyrazole Metabolites
Glutathione conjugate M-15
Polar Conjugates
Highly Polar Metabolites
Multiple components
M-3
Isox Metabolite D (RT~11)
RT5 574 MW?
Isox cys (M-26) Not Detected
RT 24 Acidic Organosoluble
M-9
Isox Metabolite B (RT~9)
Malonyl conjugation
Isox Metabolite E/P2 (RT16) = M-28
M-1
Demethylation
RT 26 minute metabolite M-9 Malonyl glucose conjugate
Isox Metabolite A (RT~7)
Oxidation
Isox Metabolite P1 (RT~8)
(M-25)
desmethyl M-1
Isox Metabolite C (RT~10) possibly forms through hydroxylation of carbon adjacent to sulfur

In general, the metabolism in rotational crops appears to occur via cleavage between the parent sulfone and isoxazoline ring and reaction of glutathione with the isoxazole ring to form a transitory glutathione conjugate (M15, not observed). Subsequent oxidation and/or demethylation of the pyrazole cleavage product occurred, yielding metabolites M1, M3, M9, and M25; metabolite M9 was further conjugated to yield a malonyl glucose conjugate. The transitory glutathione conjugate was further conjugated to another transitory metabolite (M26, not observed), which underwent further conjugation with malonate and/or glucose to form metabolites A, B, C, D, and M28; oxidation of M28 would yield metabolite P-1. Finally, hydroxylation of pyroxasulfone would yield metabolite M6.

CROP FIELD TRIALS On Corn (field and sweet)	**PMRA#s 1817269, 1817274 and 2041493**

A total of 22 trials were conducted in/on field corn in the US (one trial in each of Zones 2 and 6; 2 trials in Zone 1; 18 trials in Zone 5). A total of 12 trials were conducted in/on sweet corn (one trial in each of Zones 2, 3, 10, 11 and 12; 2 trials in Zone 1; 5 trials in Zone 5). A single post-emergence application was made at rates related to the soil type: 166 g a.i./ha for coarse soil and 299 g a.i./ha for medium and fine soil.

At three additional trials with three different soil types (fine, medium, and coarse), five different application types were compared: (1) pre-plant surface application; (2) pre-plant incorporated application; (3) post-planting pre-emergence application; (4) early post-emergence application; and (5) split pre-emergence and post-emergence applications. The application rates for types (1), (2), (3), and (4) were 300, 209, and 166 g a.i./ha for fine, medium, and coarse soils, respectively. The split application (5) was made at 200 + 100, 140 + 69, and 110 + 56 g a.i./ha for fine, medium, and coarse soils, respectively.

Commodity	PHI (days)	Combined Residues of Pyroxasulfone and the metabolites M1, M3 and M25 (ppm)[1]							
		n	Min.	Max.	LAFT[2]	HAFT[2]	Median	Mean	Std. Dev.
Application Rates: 166-300 g a.i./ha (0.148-0.268 lb a.i./A)[3]									
Field corn forage	37-95	44	<0.025	<0.055	<0.025	<0.055	0.025	0.028	0.007
Field corn grain	69-146	43	<0.025	<0.025	<0.025	<0.025	<0.025	<0.025	0
Field corn stover	85-146	44	<0.025	<0.139	<0.025	<0.131	0.025	0.032	0.02

Sweet corn forage	43-97	24	<0.025	<0.063	<0.025	<0.063	0.031	0.035	0.01
Sweet corn K+CWHR)	43-132	24	<0.025	<0.028	<0.025	<0.028	0.025	0.026	0.0007
Sweet corn stover	70-132	24	<0.025	<0.115	<0.025	<0.112	0.025	0.041	0.03
Commodity	PHI (days)	Combined Residues of Pyroxasulfone and M3 (ppm)[1]							
		n	Min.	Max.	LAFT[2]	HAFT[2]	Median	Mean	Std. Dev.
Field corn grain	69-146	43	<0.013	<0.013	<0.013	<0.013	<0.013	<0.013	0
K+CWHR	43-132	24	<0.013	<0.016	<0.013	<0.015	0.013	0.013	0.0007

[1] Except for Min/Max, values reflect per trial averages; The calculations were performed assuming LOQ residues for residues <LOQ. Total residues were calculated as parent equivalent based on the conversion factors: 1.262 for M1. 1.504 for M3 and 1.321 for M25.

[2] LAFT = lowest-average field trial; HAFT = highest-average field trial.

[3] Applications were made at early post-emergence of the crops (~V4 growth stage). Actual application rates ranged 97.6-102.9% of the target rate.

RESIDUE DECLINE In Corn	PMRA#s 1817269, 1817274, and 2041493

In the residue decline trials for corn, duplicate forage samples were collected 0, 3, 7, 15-16, 21, 29-30, 40, and 60 days following application; duplicate samples of field corn grain and stover were collected at normal harvest and 15 and 30 days after normal harvest, and duplicate samples of sweet corn K+CWHR and stover were collected at normal harvest and 7 and 14 days following normal harvest.

The decline trials showed that the total residues of pyroxasulfone (pyroxasulfone, M1 and M3) in/on forage decreased with increasing PHIs. Residues of pyroxasulfone, M1, M3, and M25 were below the LOQ in/on all field corn grain and sweet corn K+CWHR samples from the decline trials. No quantifiable residues of pyroxasulfone, M1, M3, or M25 were found in corn stover from the decline trials, except 0.007 ppm M3 at 15 days after normal harvest from one field corn trial, and 0.010 ppm declining to 0.006 ppm M1 (over the decline period of 30 days after normal harvest) from the other field corn trial.

STORAGE STABILITY (Corn)	PMRA#s 1817269, 1817274, 1817277, 1817280 and 2041493

Pyroxasulfone and metabolites M3 and M1 were found to be stable in corn stover through 12 months of frozen storage and in corn grain and forage through 13 months of frozen storage. Pyroxasulfone, M1, and M3 were found to be stable in corn processed commodities during 6 months (oil) or 7 months (starch, flour, and meal) of frozen storage. M25 residues were stable in forage for 24 months, grain for 26 months, stover for 25 months, starch for 16 months, flour for 23 months, and meal for 18 months. M25 residues in corn oil were moderately stable at 67% remaining after 17 months of frozen storage.

The freezer storage stability data for pyroxasulfone residues (pyroxasulfone, M1, M3, and M25) cover the longest storage period in field trials and processing studies for corn.

STORAGE STABILITY (Cattle Matrices)	PMRA # 1743704

Samples of cattle milk, muscle, liver, kidney, and fat were spiked with pyroxasulfone, M1, and M3 at 0.01 ppm each for milk and 0.10 ppm each for tissues. The spiked samples were stored frozen (temperature unspecified) for periods of 189 days for milk, 112 days for muscle, up to 120 days for liver, 113 days for kidney, and 91 days for fat. The study was conducted concurrently with the cattle feeding study.

The data indicate that residues of pyroxasulfone, Ml, and M3 are stable through 6 months of frozen storage in milk, 3 months of frozen storage in fat, and 3.7 months of frozen storage in muscle and kidney. Residues of M1 and M3 were stable in liver during up to 4 months of frozen storage. Pyroxasulfone was found to degrade in liver, yielding 40% recovery after 120 days of frozen storage. Short-term storage stability was adequate for pyroxasulfone in liver, where 94% was recovered after 15 days of frozen storage.

Degradation in Cattle Liver		
Analyte	Storage interval (days)	Percent decline
Pyroxasulfone	120	60%

PROCESSED FOOD AND FEED (Corn)	PMRA# 1817269, 1817274, 1817277 and 1817280
As the residues of pyroxasulfone, M1 and M3 were all < LOQ (<0.005 ppm, or <0.01 for M3 in corn meal and M1 in corn oil) in corn grain (treated at 5x GAP) and the processed commodities, no processing factor for corn could be calculated.	

LIVESTOCK FEEDING – Dairy Cattle	PMRA # 1743704
The magnitude of the residue of pyroxasulfone and metabolites M1 and M3 in dairy cow tissues and milk was determined in a feeding study. For 28 consecutive days, lactating dairy cows were administered pyroxasulfone at a target dose level of 1.8 ppm, 5.4 ppm and 18 ppm. A total of 14 cows were included in the study with two in control, three each in low and medium dose groups, and six in high dose group. The dose levels of 1.8, 5.4, and 18 ppm represent 90x, 270x, and 900x, respectively, the more balanced diet to beef cattle and 60x, 180x, and 600x, respectively, the maximum estimated dietary burden to dairy cattle.	

Commodity	Feeding level (ppm)	Maximum Residues (Pyroxasulfone) (ppm)	MBD (ppm) Dairy Cattle	Anticipated Residue at MBD (ppm)
				Dairy
Milk (Day 7, the highest)	18	<0.004	0.03	<6.7x10-7
Skimmed Milk		<0.001		<1.7x10-6
Cream		<0.001		<1.7x10-6
Round Muscle		<0.01		<1.7x10-5
Lion Muscle		<0.01		<1.7x10-5
Liver		<0.02		<3.4x10-5
Kidney		<0.01		<1.7x10-5
Subcutaneous Fat		<0.01		<1.7x10-5
Abdominal fat		<0.01		<1.7x10-5
Perinephric Fat		<0.01		<1.7x10-5

Proposed Maximum Residue Limits	
Commodity	Proposed MRL (ppm)
Field corn	0.015
Popcorn grain	0.015
Sweet corn kernels plus cob with husks removed	0.015
Eggs	0.01
Fat, meat and meat by-products of cattle, goats, hogs, horses, poultry, and sheep	0.01
Milk	0.001

Table 7 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT	Pyroxasulfone and the metabolite M3
RESIDUE DEFINITION FOR RISK ASSESSMENT	Pyroxasulfone and the metabolite M3
METABOLIC PROFILE IN DIVERSE CROPS	The metabolic profile is different in field corn and soybean

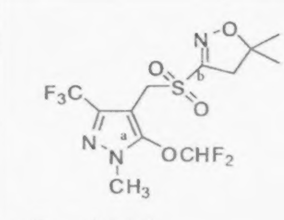
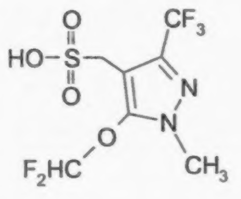
ANIMAL STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT		Pyroxasulfone	
RESIDUE DEFINITION FOR RISK ASSESSMENT			
METABOLIC PROFILE IN ANIMALS		The metabolic profile is similar in goat, hen and rats.	
FAT SOLUBLE RESIDUE		No	
DIETARY RISK FROM FOOD ONLY			
Basic chronic non-cancer dietary risk ADI = 0.02 mg/kg bw/day EEC = 268 □g a.i./L, Level I	POPULATION	ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)	
		Food Alone	Food and Water
	Total population	0.3	28.6
	All infants < 1 year	0.3	92.9
	Children 1–2 years	0.8	42.7
	Children 3 to 5 years	0.7	40.0
	Children 6–12 years	0.5	27.6
	Youth 13–19 years	0.4	20.8
	Adults 20–49 years	0.3	26.6
	Adults 50+ years	0.2	27.9
	Females 13 to 49 yrs	0.2	26.5
Basic acute non-cancer dietary risk ARfD = 0.10mg/kg bw/day EEC = 270 □g a.i./L, Level I	POPULATION	ESTIMATED RISK (95th Percentile) % of Acute Reference Dose (ARfD)	
		Food Alone	Food and Water
	Total population	0.17	14.20
	All infants < 1 year	0.27	53.14
	Children 1–2 years	0.31	22.37
	Children 3 to 5 years	0.29	20.36
	Children 6–12 years	0.22	14.19
	Youth 13–19 years	0.16	11.51
	Adults 20–49 years	0.12	13.13
	Adults 50+ years	0.08	11.84
	Females 13 to 49 yrs	0.11	13.17

Table 8 Physical and Chemical Properties of Pyroxasulfone

Property	Result	Comment
Vapour pressure at 20°C	2.4 x 10^{-6} Pa at 25°C	Relatively non-volatile under field conditions.
Henry's law constant at 20°C	2.65 x 10^{-9} atm m^3/mol	Non-volatile from moist soil or water surfaces. Laboratory studies on volatilization are not required.

Property	Result	Comment
Ultraviolet (UV) / visible spectrum	pH 1.13 λ_{max} = 222.5 nm pH 7.23 λ_{max} = 222.0 nm pH 10.91 λ_{max} = 222.5 nm	Not likely to phototransform
Solubility in water at 20°C	3.49 mg/L	Low solubility
n-Octanol/water partition coefficient (Kow)	pH 8.7: K_{OW} = 244 log K_{OW} = 2.39	Limited Potential for bioaccumulation (<3)
Dissociation constant	N/A	Determining the dissociation constant in water for Pyroxasulfone is not required because the N-containing rings are not expected to be protonated in a practical pH range.
Stability (temperature, metal)	Showed no signs of degradation at elevated temperatures to any of the metals/metal ions tested.	

Table 9 Table of Maximum Formation of Transformation Products (KIH-485 = Pyroxasulfone)

Code	Chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length)
PARENT					
KIH-485	3-[(5-(difluoromethoxy)-1-methyl-3-(trifluoromethyl) pyrazol-4-ylmethylsulfonyl]-4,5-dihydro-5,5-dimethyl-1,2-oxazole	 a : Pyrazole label b : Isoxazoline label			
MAJOR (>10%) TRANSFORMATION PRODUCTS					
KIH-485-M-1	(5-difluoromethoxy-1-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanesulfonic acid		Aerobic soil - Study 1	49 (365)	49 (365)
			Aerobic soil - Study 2	35.9 (365)	35.9 (365)
			Anaerobic soil – Soil Anaerobic soil – Water Anaerobic soil – Whole system	20.8 (365) 25.5 (365) 46.3 (365)	20.8 (365) 25.5 (365) 48.3 (365)
			Soil photolysis	ND	
			Aqueous photolysis	ND	
			Hydrolysis	ND	
			Aerobic aquatic – Water Aerobic aquatic – Sediment Aerobic aquatic – Whole system	14.9 (365) 1.2 (365) 16.1 (365)	14.9 (365) 1.2 (365) 16.1 (365)
			Anaerobic aquatic – Water Anaerobic aquatic – Sediment Anaerobic aquatic – Whole system	10.7 (365) 9.9 (365) 20.6 (365)	10.7 (365) 9.9 (365) 20.6 (365)
			Field studies – Terrestrial		

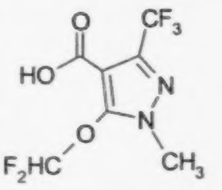
Code	Chemical name	Chemical structure	Study	Max %AR (day)	%AR at study end (study length)
			Field studies – Aquatic		
			Other	NA	NA
MINOR (<10%) TRANSFORMATION PRODUCTS					
KIH-485-M-3	5-difluoromethoxy-1-methyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic Acid		Aerobic soil - Study 1	7.1 (90)	0.8 (365)
			Aerobic soil - Study 2	10.1 (181)	6.6 (365)
			Aerobic soil - Study 3 (done with M-1)	16.3 (14)	1.1 (365)
			Anaerobic soil – Soil Anaerobic soil – Water Anaerobic soil – Whole system	4.0 (365) 6.3 (365) 10.2 (365)	4.0 (365) 6.3 (365) 10.2 (365)
			Soil photolysis	ND	ND
			Aqueous photolysis	ND	ND
			Hydrolysis	ND	ND
			Aerobic aquatic – Water Aerobic aquatic – Sediment Aerobic aquatic – Whole system	7.9 (365) 4.9 (365) 12.8 (365)	7.9 (365) 4.6 (365) 12.8 (365)
			Anaerobic aquatic – Water Anaerobic aquatic – Sediment Anaerobic aquatic – Whole system	4.9 (181) 1.7 (365) 6.5 (181)	3.6 (365) 1.7 (365) 5.3 (365)
			Field studies – Terrestrial Field studies – Aquatic		
			Other	NA	NA

Table 10 Fate and Behaviour in the Environment of Pyroxasulfone (KIH-485) and its major transformation product KIH-485-M-1

Property	Test substance	Value	Transformation products	Comments	PMRA#
Terrestrial					
Abiotic transformation					
Hydrolysis	KIH-485	pH<9 : stable pH 9= 385 days		Not important route of degradation	1743507
Phototransformation on soil	KIH-485	DT_{50} = 280 days DT_{90} = 929 days		Not important route of degradation	1743729
Phototransformation in air	N/A	N/A	N/A	N/A	N/A
Biotransformation					
Biotransformation in aerobic soil	KIH-485	DT_{50}: 145	KIH-485-M-1	Moderately persistent	1743726
	KIH-485	DT_{50}: 162-506 days	KIH-485-M-1	Moderately persistent to persistent	1743727
	KIH-485-M-1	DT_{50}: 3230 – 27200 days		Persistent	1743731
Biotransformation in anaerobic soil	KIH-485	DT_{50}: 81.6 – 160 days	KIH-485-M-1 CO_2	Moderately persistent	1743728
Mobility					
Adsorption / desorption in soil	KIH-485	Kd : 1.6 – 4.3 Koc: 54.9 – 118.8		Highly mobile	1743750
Soil leaching	KIH-485	Kd : 0.6 - 1.98 Koc: 100.1 – 210.1		Medium to High mobility	1743754
	KIH-485-M-1	Kd : 0.57 – 0.82 Koc: 41.3 – 139.6		High to very high mobility	1743755

Property	Test substance	Value	Transformation products	Comments	PMRA#
Volatilization	KIH-485	VP : 2.4×10^{-6} Pa at 25°C Henry's law: 2.65×10^{-9} atm m^3/mol	N/A	Not likely to volatilize	N/A
Field studies					
Terrestrial field dissipation	KIH-485	$DT_{50} = 4 - 35$ days $DT_{90} = 32 - 116$		Non to slightly persistent	1743734
Field leaching	N/A	N/A	N/A	N/A	N/A
Aqueous					
Abiotic transformation					
Phototransformation in water	KIH-485	Irradiated $DT_{50} = 119$ days $DT_{90} = 396$ days Non-irradiated $DT_{50} = 15900$ days $DT_{90} = 52700$ days		Not important route of degradation	1743508
Biotransformation					
Biotransformation in aerobic water systems	KIH-485	Water DT_{50} : 48 days DT_{90} : 234 days Sediment DT_{50} : 183 days DT_{90} : 609 days Whole system DT_{50} : 117 days DT_{90} : 389 days	Water KIH-485-M-1 & CO_2 Sediment KIH-485-M-1 Whole system KIH-485-M-1 KIH-485-M-3	Moderately persistent to persistent	1743757
Biotransformation in anaerobic water systems	KIH-485	Water DT_{50} : 51.6 days DT_{90} : 171 days Sediment DT_{50} : 82.2 days DT_{90} : 273 days Whole system DT_{50} : 70.5 days DT_{90} : 234 days	Water KIH-485-M-1 & CO_2 Sediment KIH-485-M-1 Whole system KIH-485-M-1	Moderately persistent to persistent	1743758
Field studies					
Flooded field dissipation	KIH-485	Water $DT_{50} = 0.022 - 0.67$ days $DT_{90} = 0.95 - 2.22$ days Soil $DT_{50} = 1.34 - 3.17$ days $DT_{90} = 4.45 - 10.5$ days		Non persistent	1743772

Table 11 Toxicity of Pyroxasulfone TGAI (KIH-485) to Non-Target terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Earthworm	14d-Acute	KIH-485	LC_{50} > 997 mg a.i./kg dry soil		1743816
Eisenia fetida	Chronic	KIH-485	NOEC = 1000 mg a.i./kg dry soil		1845490
Bee *Apis mellifera*	48h-Contact	KIH-485	LD_{50} > 100 µg/bee (equivalent to 112 kg a.i./ha)	Relatively non-toxic	1743811
Predatory arthropod *Typhlodromus pyri*	7d-Contact	KIH-485	ER_{50} > 1000 mg a.i./ha		1743815 1817234
Parasitic arthropod *Aphidius rhopalosiphi*	48h-Contact	KIH-485	ER_{50} > 1000 mg a.i./ha		1817283 1817235
Birds					
Bobwhite quail *Colinus virginianus*	Acute	KIH-485	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic	1743773
	Dietary	KIH-485	LD_{50} > 1348.8 mg a.i./kg bw/day	Practically non-toxic	1743777
	Reproduction	KIH-485	NOEL = 89.24 mg a.i./kg bw/day	-	1743781
Zebra finch *Poephila guttata*	Acute	KIH-485	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic	1743775
Mallard duck *Anas platyrhynchos*	Dietary	KIH-485	LD_{50} > 2448.3 mg a.i./kg bw/day	Practically non-toxic	1743779
	Dietary	KIH-485	NOEL = 416.7 mg a.i./kg bw/day	-	1743779
	Reproduction	KIH-485	NOEL = 8.37 mg a.i./kg bw/day LOEL = 33.7 mg a.i./kg bw/day	-	1743782
Mammals					
Rat	Acute	KIH-485	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	1743534
	One-generation (supp. Range finding study)	KIH-485	NOEL: 1.69 mg a.i./kg bw/day LOEL: 16.0 mg a.i./kg bw/day	-	1743618
	Multi-generation reproduction	KIH-485	NOEL = 5.75 mg a.i./kg bw/day LOEL = 114.24 mg a.i./kg bw/day	-	1743620
Vascular plants					
Vascular plant	21d-Seedling emergence	KIH-485	Onion (*Allium cepa*) EC_{25} = 75 NOEC = 37.5 g a.i./ha		1743789
	21d-Vegetative vigour	KIH-485	Pumpkin (*Cucurbita mixta*) EC_{25} = 92 NOEC = 18.8 g a.i./ha		1743790

Table 12 Screening level risk assessment on terrestrial invertebrates exposed to Pyroxasulfone 85WG at a rate of 247 g a.i./ha on field corn

Organism	Exposure	Endpoint value/UF[a]	EEC	RQ	Exceeds LOC
Earthworm	Acute	> 498.5 mg a.i./kg	0.1098 mg a.i./kg	< 0.0002	No
Bee	Contact	> 112 kg a.i./kg	247 g a.i./ha	< 0.002	No
Predatory arthropod	Contact	LR_{50}: >1000 g a.i./kg ER_{50}: >1000 g a.i./kg	247 g a.i./ha	< 0.3	No
Parasitic arthropod	Contact	LR_{50}: >1000 g a.i./kg ER_{50}: >1000 g a.i./kg	247 g a.i/ha	< 0.3	No

a UF = uncertainty factor applied to the endpoints: Earthworms 0.5; Honeybees 1; Predatory and parasitoid arthropods 1

Table 13 Maximum and mean residue Estimated Environmental Concentrations (EEC) on food items following a single application of Pyroxasulfone WG85 at a rate of 247 g a.i./ha on field corn

	Maximum residue concentrations			Mean residue concentrations		
Matrix	EEC[a] (mg ai/kg fw)	fresh/dry weight ratios	EEC (mg ai/kg dw)	EEC[a] (mg ai/kg fw)	fresh/dry weight ratios	EEC (mg ai/kg dw)
short range grass	52.8591	3.3[b]	174.44	18.7724	3.3[b]	61.95
leaves and leafy crops	29.8870	11[b]	328.76	9.8800	11[b]	108.00
long grass	24.2060	4.4[b]	106.51	7.9040	4.4[b]	34.78
forage crops	29.8870	5.4[b]	161.39	9.8800	5.4[b]	53.35
small insects	12.8440	3.8[c]	48.81	7.1630	3.8[c]	27.22
pods with seeds	3.2110	3.9[c]	12.53	1.5314	3.9[c]	5.97
large insects	3.2110	3.8[c]	12.20	1.5314	3.8[c]	5.82
grain and seeds	3.2110	3.8[c]	12.20	1.5314	3.8[c]	5.82
fruit	3.2110	7.6[c]	24.40	1.5314	7.6[c]	11.64

a Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
b Fresh / dry weight ratios from Harris (1975)
c Fresh / dry weight ratios from Spector (1956)

Table 14 Screening level risk assessment on birds following a single application of Pyroxasulfone W85 at a rate of 247 g a.i./ha on field corn.

	Endpoint	Study Endpoint (mg ai/kg bw/day / UF[a])	Feeding Guild[b] (food item)	EDE[c] (mg ai/kg bw)	RQ	LOC Exceeded
Screening level						
Acute	20 g	225.0	Insectivore (small insects)	12.45	0.06	No
	100g			9.77	0.04	No
	1000g		Herbivore (Short grass)	10.19	0.05	No
Reproduction NOEL	20 g	8.37	Insectivore (small insects)	12.52	**1.49**	**Yes**
	100g			9.77	**1.16**	**Yes**
	1000g		Herbivore (Short grass)	10.19	**1.21**	**Yes**
Further characterization						
Reproduction LOEL	20 g	33.72	Insectivore (small insects)	12.45	0.37	No
	100g			9.71	0.29	No
	1000g		Herbivore (Short grass)	10.13	0.30	No

[a] UF = uncertainty factor applied to the endpoints: Acute = 0.1, NOEL = 1
[b] At the screening level, food items representing the most conservative EEC for each size guild are used
[c] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) x EEC.
Food Ingestion Rates (FIR - Nagy, 1987).
For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$

Table 15 Screening level risk assessment on mammals following a single application of Pyroxasulfone W85 at a rate of 247 g a.i./ha on field corn

	Endpoint	Study Endpoint (mg ai/kg bw/day / UF[a])	Feeding Guild[b] (food item)	EDE[c] (mg ai/kg bw)	RQ	LOC Exceeded
Screening level						
Acute	15 g	200	Insectivore (small insects)	7.16	0.04	No
	35 g		Herbivore (Short grass)	22.43	0.1	No
	1000 g			11.98	0.06	No
Reproduction NOEL	15 g	5.75	Insectivore (small insects)	7.16	**1.2**	**Yes**
	35 g		Herbivore (Short grass)	22.43	**3.9**	**Yes**
	1000 g			11.98	**2.1**	**Yes**
Further characterization						
Reproduction LOEL	15 g	16.0	Insectivore (small insects)	6.28	0.4	No
	35 g		Herbivore (Short grass)	22.43	**1.4**	**Yes**
	1000 g			11.98	0.8	No

[a] UF = uncertainty factor applied to the endpoints: Acute = 0.1, NOEL = 1

[b] At the screening level, food items representing the most conservative EEC for each size guild are used

[c] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) x EEC.

Food Ingestion Rates (Nagy, 1987).

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{BW in g})^{0.822}$

Table 16 Refined avian reproduction risk assessment (Mallard NOEL of 8.37 mg ai/kg bw/day) exposed to maximum and mean nomogram residue concentrations following a single application of Pyroxasulfone 85WG at a rate of 247 g a.i./ha on field corn

		Maximum nomogram residues				**Mean nomogram residues**				**LOC Exceeded**
		On-field*		**Off Field**		**On-field**		**Off Field***		
Toxicity (mg ai/kg bw/d)	**Food Guild (food item)**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	
Small Bird (0.02 kg)										
8.37	Insectivore (small insects)	12.52	**1.49**	0.75	0.09	6.94	0.83	0.42	0.05	**Yes**
Medium Sized Bird (0.1 kg)										
8.37	Insectivore (small insects)	9.77	**1.16**	0.58	0.07	5.42	0.65	0.32	0.04	**Yes**
Large Sized Bird (1 kg)										
8.37	Herbivore (short grass)	10.19	**1.21**	0.61	0.07	3.60	0.43	0.22	0.03	**Yes**

* Off field EEC assuming a ground boom sprayer with medium droplet size (American Society of Agricultural Engineering (ASAE)) which can result in drift deposition of 6% the application rate (14.8 g a.i./ha) 1 meter downwind of the application

Table 17 Refined avian reproduction risk assessment (Mallard LOEL of 33.72 mg ai/kg bw/day) exposed to maximum and mean nomogram residue concentrations following a single application of Pyroxasulfone 85WG at a rate of 247 g a.i./ha on field corn

		Maximum nomogram residues				Mean nomogram residues				LOC Exceeded
		On-field		Off Field*		On-field		Off Field*		
Toxicity (mg ai/kg bw/d)	**Food Guild (food item)**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	
Small Bird (0.02 kg)										
33.72	Insectivore (small insects)	12.52	0.37	1.38	0.04	6.98	0.21	0.77	0.02	**No**
Medium Sized Bird (0.1 kg)										
33.72	Insectivore (small insects)	9.77	0.29	1.07	0.03	5.45	0.16	0.60	0.02	**No**
Large Sized Bird (1 kg)										
33.72	Herbivore (short grass)	10.19	0.30	1.12	0.03	3.62	0.11	0.40	0.01	**No**

* Off field EEC assuming a ground boom sprayer with medium droplet size (American Society of Agricultural Engineering (ASAE)) which can result in drift deposition of 6% the application rate (14.8 g a.i./ha) 1 meter downwind of the application

Table 18 Refined mammalian reproduction risk assessment (rat NOEL of 5.75 mg ai/kg bw/day) exposed to maximum and mean nomogram residue concentrations following a single application of Pyroxasulfone 85WG at a rate of 247 g a.i./ha on field corn

	Maximum nomogram residues				Mean nomogram residues				LOC Exceeded
	On-field		Off Field*		On-field		Off Field*		
Food Guild (food item)	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	**EDE (mg ai/kg bw)**	**RQ**	
Small Mammal (0.015 kg)									
Insectivore (small insects)	7.2	**1.2**	0.4	0.1	4.0	0.7	0.2	0.0	**Yes**
Granivore (grain and seeds)	1.8	0.3	0.1	0.0	0.9	0.1	0.1	0.0	No
Frugivore (fruit)	3.6	0.6	0.2	0.0	1.7	0.3	0.1	0.0	No
Medium Sized Mammal (0.035 kg)									
Insectivore (small insects)	6.3	**1.1**	0.4	0.1	3.5	0.6	0.2	0.0	**Yes**
Insectivore (large insects)	1.6	0.3	0.1	0.0	0.7	0.1	0.0	0.0	No
Granivore (grain and seeds)	1.6	0.3	0.1	0.0	0.7	0.1	0.0	0.0	No
Frugivore (fruit)	3.1	0.5	0.2	0.0	1.5	0.3	0.1	0.0	No
Herbivore (short grass)	22.4	**3.9**	1.3	0.2	8.0	**1.4**	0.5	0.1	**Yes**
Herbivore (long grass)	13.7	**2.4**	0.8	0.1	4.5	0.8	0.3	0.0	**Yes**
Large Sized Mammal (1 kg)									
Insectivore (small insects)	3.4	0.6	0.2	0.0	1.9	0.3	0.1	0.0	No
Insectivore (large insects)	0.8	0.1	0.1	0.0	0.4	0.1	0.0	0.0	No
Granivore (grain and seeds)	0.8	0.1	0.1	0.0	0.4	0.1	0.0	0.0	No
Frugivore (fruit)	1.7	0.3	0.1	0.0	0.8	0.1	0.0	0.0	No
Herbivore (short grass)	12.0	**2.1**	0.7	0.1	4.3	0.7	0.3	0.0	**Yes**
Herbivore (long grass)	7.3	**1.3**	0.4	0.1	2.4	0.4	0.1	0.0	**Yes**

* Off field EEC assuming a ground boom sprayer with medium droplet size (American Society of Agricultural Engineering (ASAE)) which can result in drift deposition of 6% the application rate (14.8 g a.i./ha) 1 meter downwind of the application

Table 19 Estimated environmental concentration (EEC) and risk assessment for non-target terrestrial plants following a single application of Pyroxasulfone W85 at a rate of 247 g a.i./ha on field corn

Organism	Exposure	Endpoint value	EEC (g a.i./ha)	RQ	LOC Exceeded
Onion	Vegetative vigour	75 g a.i./ha	247[1]	3.3	**Yes**
			14.8[2]	0.2	No

[1] EEC calculated assuming direct application to plant

[2] EEC calculated assuming a ground boom sprayer with medium droplet size producing drift deposition 1 meter downwind of the application site of 6% the application rate American Society of Agricultural Engineering (ASAE)

Table 20 Toxicity of Pyroxasulfone TGAI (KIH-485) to Non-Target aquatic Species

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Freshwater Invertebrates					
Daphnia *Daphnia magna*	48-h Acute	KIH-485	LC_{50}: >4.4 NOEC: 4.4	Moderately toxic*	1743795
	21-d chronic	KIH-485	NOEC: 1.9	*	1743796
Freshwater Fish					
Rainbow trout *Oncorhynchus mykiss*	96-h Acute	KIH-485	LC_{50} > 2.2 NOEC : 2.2	Moderately toxic*	1743792
Bluegill sunfish *Lepomis macrochirus*	96-h Acute	KIH-485	LC_{50} > 2.8 NOEC: 2.8	Moderately toxic*	1743793
Fathead minnow *Pimephales promelas*	ELS	KIH-485	NOEC: 2.0 LOEC: 3.9 (length)	-	1743794
Freshwater Plants					
Algae *Pseudokirchneriella subcapitata*	72-h Acute	KIH-485	E_bC_{50} (72h): 0.000317 NOEC: 0.00005	-	1743797
		KIH-485 – M1	E_xC_{50}: 44-66 NOEC: 31	-	1743801
		KIH-485 – M3	E_XC_{50}: 43-46 NOEC: 15	-	1743802
Anabaena flos-aquae	96-h	KIH-485	E_xC50 (72- 96-h) > 3.5 (highest concentration tested) NOEC (72-h) = 0.80 (cell density) NOEC (96-h) = 0.80 (cell density, biomass)	-	1743798
Navicula pelliculosa	96-h Acute toxicity	KIH-485	E_xC50 (72- 96-h) > 3.2 NOEC (72- 96h) = 3.2 (highest concentration tested)	-	1743799
Vascular plants *Lemna gibba*	7-d Acute	KIH-485	Growth rate EC_{50} 0.0161 Frond number EC_{50} 0.005 Biomass EC_{50} 0.0096 NOEC (biomass) : 0.00043 mg a.i./L	-	1743803
		KIH-485 – M1	EC_{50} > 123 NOEC > 123 (highest concentration tested)	-	1743804
		KIH-485 – M3			1743810
Marine invertebrates					
Saltwater Mysid *Americamysis bahia*	96-h Acute	KIH-485	LC_{50} >1.4 NOEC: 1.4	Moderately toxic*	1743787
Eastern Oyster *Crassostrea virginica*	96-h Acute (Shell deposition)	KIH-485	EC_{50} > 3.6 NOEC: 3.6		1743786
Marine fish					
Sheepshead Minnow *Cyprinodon variegatus*	96-h Acute	KIH-485	LC_{50} > 3.3 NOEC: 3.3		1743788
Marine algae					

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Marine Diatom *Skeletonema costatum*	96-h Acute	KIH-485	E_bC_{50} (72h): 0.49 E_bC_{50} (96h): 0.61 NOEC: 0.14 (Biomass and growth rate)	-	1743800

* no observed effects at highest tested concentration. A.i. has low solubility in water (3.49 mg ai/L)

Table 21 Screening level risk assessment on aquatic non-target organisms following a single application of Pyroxasulfone W85 at a rate of 247 g a.i./ha on field corn

Organism	Exposure	Endpoint value (mg a.i./L)	EEC (mg a.i./L)	RQ	LOC Exceeded
Freshwater species					
Daphnia magna	Acute	LC_{50}>4.4[1]	0.031[a]	0.01	No
	Chronic	NOEC:1.9		0.02	No
Rainbow trout	Acute	LC_{50}>2.2[2]		0.1	No
Fathead minnow	ELS	NOEC: 2.0		0.02	No
Bluegill sunfish	Acute	LC_{50}>2.8[2]		0.1	No
Amphibians (acute rainbow trout as surrogate)	Acute	LC_{50}>2.2[2]	0.17[b]	0.8	No
Freshwater alga *Pseudokirchneriella subcapitata*	Acute	KIH-485: E_bC_{50}(72h): 0.000317[1] KIH-485-M1: E_bC_{50}(72h): 44[1] KIH-485-M3: E_bC_{50}(96h): 43[1]	0.031[a]	**195** 0.001 0.002	**Yes** No No
Anabaena flos-aquae	Acute	E_xC_{50}:>3.5[1]		0.02	No
Navicula pelliculosa	Acute	E_xC_{50}:>3.2[1]		0.02	No
Vascular plant - *Lemna gibba*	Acute	KIH-485: EC_{50} (frond number): 0.005[1] KIH-485-M1: EC_{50}>123[1] KIH-485-M3: EC_{50}>123[1]		**12.4** 0.0005 0.0005	**Yes** No No
Marine species					
Crustacean	Acute	LC_{50}>1.4[1]	0.031[a]	0.04	No
Mollusk	Acute	EC_{50}> 3.6[1]		0.02	No
Sheepshead minnow	Acute	LC_{50}>3.3[2]		0.09	No
Marine alga *Skeletonema costatum*	Acute	EbC50 (72h):0.49[1]		0.1	No

To account for differences in species sensitivity as well as varying protection goals (for example, community, population, individual) acute endpoints are multiplied by the following uncertainty factor:

1) 0.5
2) 0.1
a) The EECs are calculated for 80cm deep water bodies
b) The EECs for amphibians are calculated for 15cm deep water bodies

Table 22 Tier I risk assessment for aquatic organisms exposed to spray drift and runoff following a single application of Pyroxasulfone 85WG at a rate of 247 g a.i./ha on field corn

Organism	Exposure	Endpoint value[1] (mg a.i./L)	Drift (6% spray deposition)			Run-off[b]		
			EEC[a] (mg a.i./L)	RQ	LOC exceeded	EEC[a] (mg a.i./L)	RQ	LOC exceeded
Freshwater alga - *Pseudokirchneriella subcapitata*	Acute	E_bC_{50}(72h): 0.000317	0.0019	**12.0**	**Yes**	0.00047 - 0.023	**2.97-145.1**	**Yes**
Vascular plant - *Lemna gibba*	Acute	EC_{50} (frond number): 0.005		0.7	No		0.2 – **9.2**	**Yes**

[1] To account for differences in species sensitivity as well as varying protection goals (for example, community, population, individual), an uncertainty factor of 0.5 is applied to acute endpoints

a) The EECs are calculated for 80cm deep water bodies

b) 96h EECs from water modelling, range for all scenarios (see Table 3)

Table 23 Level 1 aquatic ecoscenario modelling (runoff) EECs (µg a.i./L) for pyroxasulfone in a water body 80 cm deep following a single application of Pyroxasulfone 85WG at a rate of 247 g a.i./ha, excluding spray drift

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
British Columbia	0.48	0.47	0.43	0.41	0.40	0.27
Alberta	8.9	8.7	8.1	7.1	6.6	4.3
Manitoba	12	11	11	10	9.7	6.6
Ontario	10	10	9.5	8.5	7.9	5.1
Quebec	17	16	16	15	14	8.5
Prince Edward Island	23	23	21	20	18	11

Table 24 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Pyroxasulfone TGAI Endpoints	Pyroxasulfone – M-1 Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	DT_{50}: 145-506 days	DT_{50}: 3230 – 27200 days
	Water	Half-life ≥ 182 days	DT_{50}: 48 days	Value not available
	Sediment	Half-life ≥ 365 days	DT_{50}: 183 days	Value not available
	Air	Half-life ≥ 2 days or evidence of long range	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is	Value not available

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Pyroxasulfone TGAI Endpoints	Pyroxasulfone – M-1 Endpoints
		transport	unlikely to occur based on the vapour pressure (2.4×10^{-6} Pa) and Henry's Law Constant (2.65×10^{-9} atm·m^3/m).	
Bioaccumulation[4]	Log $K_{OW} \geq 5$		Log Kow = 2.39	LogKow = -0.2[5]
	BCF ≥ 5000		Value not available	Value not available
	BAF ≥ 5000		Value not available	Value not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

[5] Value estimated using United States Environmental Protection Agency (US EPA) software EpiSuite.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Pyroxasulfone is a new active ingredient which is concurrently being registered in the US and Australia. The US EPA is in agreement with the specified Canadian MRLs and will be promulgating the same tolerances (*40 CFR Part 180*), except animal commodities. Codex MRLs[10] (*Codex MRLs* searchable by pesticide or commodity) have not been established for pyroxasulfone on any commodity. The Australia APVMA is promulgating MRLs on cereal grains and some livestock commodities.

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Australia (ppm)
Eggs	0.01	-	0.02
Fat, meat, and meat byproducts of cattle, hogs, horses, poultry and sheep	0.01	-	-
Field corn	0.015	0.015	-
Popcorn grain	0.015	0.015	-
Sweet corn (K+CWHR)	0.015	0.015	-
Milk	0.001	-	0.002

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

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[10] Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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4.0 Value

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B. Additional Information Considered

i) Published Information

1.0 Chemistry

2.0 Human and Animal Health

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3.0 Environment

4.0 Value

ii) Unpublished Information

1.0 Chemistry

2.0 Human and Animal Health

3.0 Environment

4.0 Value